AD-A212 353

ASSIFIED — MASTER COPY - FOR REPRODUCTION PURPOSES (2)

CLASSIFICATION OF THIS PAGE

DTIC ELECTE SEP 13 1989 S B

REPORT DOCUMENTATION PAGE

RT SECURITY CLASSIFICATION: Unclassified	1b. RESTRICTIVE MARKINGS
RITY CLASSIFICATION AUTHORITY	3. DISTRIBUTION/AVAILABILITY OF REPORT: Approved for public release; distribution unlimited.
ASSIFICATION/DOWNGRADING SCHEDULE	
RMING ORGANIZATION REPORT NUMBER(S)	5. MONITORING ORGANIZATION REPORT NUMBER(S): ARO 22825.7-CH
E OF PERFORMING ORGANIZATION: Ohio State University	6b. OFFICE SYMBOL (If applicable)
	7a. NAME OF MONITORING ORGANIZATION: U. S. Army Research Office
ESS (City, State, and ZIP Code): Columbus, OH 43212-1194	7b. ADDRESS (City, State, and ZIP Code): P. O. Box 12211, Research Triangle Park, NC 27709-2211
8a. NAME OF FUNDING/SPONSORING ORGANIZATION: U. S. Army Research Office	8b. OFFICE SYMBOL (If applicable)
	9. PROCUREMENT INSTRUMENT IDENTIFICATION NUMBER: DAAG29-85-K-0200
8c. ADDRESS (City, State, and ZIP Code): P. O. Box 12211, Research Triangle Park, NC 27709-2211	10. SOURCE OF FUNDING NUMBERS

PROGRAM ELEMENT NO.	PROJECT NO.	TASK NO.	WORK UNIT ACCESSION NO

11. TITLE (Include Security Classification)
The Chemistry of Hexaazatriphenylene Hexanitrile, a Polyfunctional Heterocycle With Potential Utility in the Formulation of Thermosable Polymers

12. PERSONAL AUTHOR(S)
Anthony W. Czarnik

13a. TYPE OF REPORT	13b. TIME COVERED	14. DATE OF REPORT (Year, Month, Day)	15. PAGE COUNT
Final	FROM 8/1/85 TO 7/31/89	June 1989	3+

16. SUPPLEMENTARY NOTATION
The view, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy, or decision, unless so designated by other documentation.

17. COSATI CODES		
FIELD	GROUP	SUB-GROUP

18. SUBJECT TERMS (Continue on reverse if necessary and identify by block number)
Hexaazatriphenylene Hexanitrile, Hexaazatriphenylene, Trifluoroacetic Acid, Hexacarbonitrile

19. ABSTRACT (Continue on reverse if necessary and identify by block number)

Research results are contained in the publications listed below:

K. Kanakarajan and A. W. Czarnik, "Synthesis and Some Reactions of Hexaazatriphenylene Hexanitrile, a Hydrogen-Free Polyfunctional Heterocycle with D_{3h} Symmetry," *J. Org. Chem.* 1986, *51*, 5241.

M. S. P. Sarma and A. W. Czarnik, "Decarboxylative Synthesis of Hexaazatriphenylene", *Synthesis* 1988, 72.

K. Kanakarajan, K. Haider, and A. W. Czarnik, "Nitrosations in Anhydrous Trifluoroacetic Acid Media: A Modification for Insoluble or Deactivated Amine and Amide Precursors", *Synthesis* 1988, 566

(over)

20. DISTRIBUTION/AVAILABILITY OF ABSTRACT	21. ABSTRACT SECURITY CLASSIFICATION
☐ UNCLASSIFIED/UNLIMITED ☐ SAME AS RPT. ☐ DTIC USERS	Unclassified

22a. NAME OF RESPONSIBLE INDIVIDUAL	22b. TELEPHONE (Include Area Code)	22c. OFFICE SYMBOL

DD FORM 1473, 84 MAR — 83 APR edition may be used until exhausted. All other editions are obsolete.

SECURITY CLASSIFICATION OF THIS PAGE
UNCLASSIFIED

89

K. Kanakarajan and A. W. Czarnik, "Materials Derived from the Hydrogen-Free Heterocycle Hexaazatriphenylene Hexacarbonitrile. Syntheses and High Temperature Properties of Polyimides", in *Society of Advanced Materials and Process Engineering Series* 1988, *33*, 956. [no reprints remaining]

K. Kanakarajan and A. W. Czarnik, "A Highly Crosslinked, Thermally Stable Polyimide Film Derived From Hexaazatriphenylene"; *Polymer Preprints* 1988, *29*, No. 1, 246. [no reprints remaining]

K. Kanakarajan and A. W. Czarnik, "Syntheses of Some Hexacarboxylic Acid Derivatives of Hexaazatriphenylene", *J. Heterocyclic Chem.* 1988, *25*, 1869.

K. Kanakarajan and A. W. Czarnik, "Synthesis and Thermogravimetric Analyses of Trisimides and Polyimides Derived from Hexaazatriphenylene", *Polymer Communications* 1989, *30*, 171

ARO 22825.7-CH

THE OHIO STATE UNIVERSITY

The Chemistry of Hexaazatriphenylene Hexanitrile, A Polyfunctional Heterocycle with Potential Utility in the Formulation of Thermostable Polymers

Anthony W. Czarnik
Department of Chemistry

Army Research Office
Research Triangle Park, North Carolina 27709

Contract No. DAAG29-85-K-0200
Final Report
RF Project 764885/717469

June 1989

PROGRESS REPORT

TWENTY COPIES REQUIRED

1. ARO PROPOSAL NUMBER: 22825-CH

2. PERIOD COVERED BY REPORT: [redacted] 31 July 1989

3. TITLE OF PROPOSAL: The Chemistry of Hexaazatriphenylene Hexanitrile, A Polyfunctional Heterocycle with Potential Utility in the ---

4. CONTRACT OR GRANT NUMBER: DAAG29-85-K-0200

5. NAME OF INSTITUTION: Ohio State University

6. AUTHORS OF REPORT: Anthony W. Czarnik

7. LIST OF MANUSCRIPTS SUBMITTED OR PUBLISHED UNDER ARO SPONSORSHIP DURING THIS REPORTING PERIOD, INCLUDING JOURNAL REFERENCES:

-see attached second page

8. SCIENTIFIC PERSONNEL SUPPORTED BY THIS PROJECT AND DEGREES AWARDED DURING THIS REPORTING PERIOD:

-none

Anthony W. Czarnik
Department of Chemistry
Ohio State University
190 West 19th Avenue
Columbus, OH 43210-1110

BRIEF OUTLINE OF RESEARCH FINDINGS

THIS IS THE FINAL REPORT FOR THIS PROJECT.

During this reporting period (Jan 89-Jun 89) one graduate student, Mr. Chris Dalton, has been working on synthetic approaches to HAT-$(NH_2)_6$. However, as the funds for this project have been completely expended, there are currently no personnel supported by this ARO project.

Seven publications, listed below, have resulted from this effort. Copies of five publications acknowledging ARO support are included with this report. We are grateful for the support we have received over the past three years, which has made our work with hexaazatriphenylene derivatives possible.

Publications:

K. Kanakarajan and A. W. Czarnik, "Synthesis and Some Reactions of Hexaazatriphenylene Hexanitrile, a Hydrogen-Free Polyfunctional Heterocycle with D_{3h} Symmetry," *J. Org. Chem.* 1986, *51*, 5241.

M. S. P. Sarma and A. W. Czarnik, "Decarboxylative Synthesis of Hexaazatriphenylene", *Synthesis* 1988, 72.

K. Kanakarajan, K. Haider, and A. W. Czarnik, "Nitrosations in Anhydrous Trifluoroacetic Acid Media: A Modification for Insoluble or Deactivated Amine and Amide Precursors", *Synthesis* 1988, 566

K. Kanakarajan and A. W. Czarnik, "Materials Derived from the Hydrogen-Free Heterocycle Hexaazatriphenylene Hexacarbonitrile. Syntheses and High Temperature Properties of Polyimides", in *Society of Advanced Materials and Process Engineering Series* 1988, *33*, 956. [no reprints remaining]

K. Kanakarajan and A. W. Czarnik, "A Highly Crosslinked, Thermally Stable Polyimide Film Derived From Hexaazatriphenylene", *Polymer Preprints* 1988, *29*, No. 1, 246. [no reprints remaining]

K. Kanakarajan and A. W. Czarnik, "Syntheses of Some Hexacarboxylic Acid Derivatives of Hexaazatriphenylene", *J. Heterocyclic Chem.* 1988, *25*, 1869.

K. Kanakarajan and A. W. Czarnik, "Synthesis and Thermogravimetric Analyses of Trisimides and Polyimides Derived from Hexaazatriphenylene", *Polymer Communications* 1989, *30*, 171

AWCzarnik

Anthony W. Czarnik
26 Jul 89

The Ohio State University
Research Foundation
1314 Kinnear Road
Columbus Ohio 43212-1194
614-292-3805

THE OHIO STATE UNIVERSITY

The Chemistry of Hexaazatriphenylene Hexanitrile, A Polyfunctional Heterocycle with Potential Utility in the Formulation of Thermostable Polymers

Anthony W. Czarnik
Department of Chemistry

Army Research Office
Research Triangle Park, North Carolina 27709

Contract No. DAAG29-85-K-0200
Final Report
RF Project 764885/717469

June 1989

PROGRESS REPORT

TWENTY COPIES REQUIRED

1. ARO PROPOSAL NUMBER: 22825-CH

2. PERIOD COVERED BY REPORT: 1 January 1989 - 30 June 1989

3. TITLE OF PROPOSAL: The Chemistry of Hexaazatriphenylene Hexanitrile, A Polyfunctional Heterocycle with Potential Utility in the ---

4. CONTRACT OR GRANT NUMBER: DAAG29-85-K-0200

5. NAME OF INSTITUTION: Ohio State University

6. AUTHORS OF REPORT: Anthony W. Czarnik

7. LIST OF MANUSCRIPTS SUBMITTED OR PUBLISHED UNDER ARO SPONSORSHIP DURING THIS REPORTING PERIOD, INCLUDING JOURNAL REFERENCES:

-see attached second page

8. SCIENTIFIC PERSONNEL SUPPORTED BY THIS PROJECT AND DEGREES AWARDED DURING THIS REPORTING PERIOD:

-none

Anthony W. Czarnik
Department of Chemistry
Ohio State University
190 West 19th Avenue
Columbus, OH 43210-1110

BRIEF OUTLINE OF RESEARCH FINDINGS

THIS IS THE FINAL REPORT FOR THIS PROJECT.

During this reporting period (Jan 89-Jun 89) one graduate student, Mr. Chris Dalton, has been working on synthetic approaches to HAT-$(NH_2)_6$. However, as the funds for this project have been completely expended, there are currently no personnel supported by this ARO project.

Seven publications, listed below, have resulted from this effort. Copies of five publications acknowledging ARO support are included with this report. We are grateful for the support we have received over the past three years, which has made our work with hexaazatriphenylene derivatives possible.

Publications:

K. Kanakarajan and A. W. Czarnik, "Synthesis and Some Reactions of Hexaazatriphenylene Hexanitrile, a Hydrogen-Free Polyfunctional Heterocycle with D_{3h} Symmetry," *J. Org. Chem.* 1986, *51*, 5241.

M. S. P. Sarma and A. W. Czarnik, "Decarboxylative Synthesis of Hexaazatriphenylene", *Synthesis* 1988, 72.

K. Kanakarajan, K. Haider, and A. W. Czarnik, "Nitrosations in Anhydrous Trifluoroacetic Acid Media: A Modification for Insoluble or Deactivated Amine and Amide Precursors", *Synthesis* 1988, 566

K. Kanakarajan and A. W. Czarnik, "Materials Derived from the Hydrogen-Free Heterocycle Hexaazatriphenylene Hexacarbonitrile. Syntheses and High Temperature Properties of Polyimides", in *Society of Advanced Materials and Process Engineering Series* 1988, *33*, 956. [no reprints remaining]

K. Kanakarajan and A. W. Czarnik, "A Highly Crosslinked, Thermally Stable Polyimide Film Derived From Hexaazatriphenylene", *Polymer Preprints* 1988, *29*, No. 1, 246. [no reprints remaining]

K. Kanakarajan and A. W. Czarnik, "Syntheses of Some Hexacarboxylic Acid Derivatives of Hexaazatriphenylene", *J. Heterocyclic Chem.* 1988, *25*, 1869.

K. Kanakarajan and A. W. Czarnik, "Synthesis and Thermogravimetric Analyses of Trisimides and Polyimides Derived from Hexaazatriphenylene", *Polymer Communications* 1989, *30*, 171

AWCzarnik

Anthony W. Czarnik
26 Jul 89

The Ohio State University
Research Foundation
1314 Kinnear Road
Columbus Ohio 43212-1194
614-292-3805

Reprinted from

polymer communications

dehydrogenated with 2,3-dichloro-5,6-dicyanobenzoquinone conducted at low temperatures by the DDQ method. Recently,

EDITORS

SUBMISSIONS

Polymer Communications is published as a supplement to **Polymer**, the monthly international journal for the science and technology of polymers. Manuscripts submitted to **Polymer Communications** from North America should be sent to the US Associate Editor, **Polymer Communications** Dr L. Smith; manuscripts from Japan should be sent to the Japanese Associate Editor, **Polymer Communications** Professor Y. Imanishi; all other manuscripts should be sent to the UK Associate Editor, **Polymer Communications** Professor R. Epton.

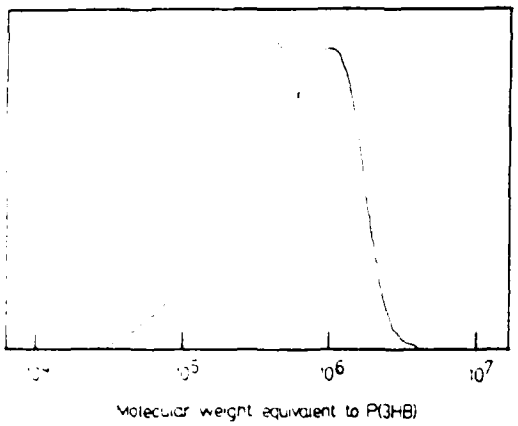


Figure 2 Molecular weight distribution curves of copolyesters. ---, Sample 1; ——, sample 9

(sample 5), were placed at 30°C in a soil collected in Yokohama, Japan. The P(3HB-*co*-17%4HB) film was completely decomposed within 2 weeks, while it took more than 10 weeks for a complete degradation of the P(3HB) film. Thus, the rate of biodegradation of P(3HB-*co*-17%4HB) film was faster than that of P(3HB) film. A detailed study of the biodegradation of microbial polyesters is in progress.

References

1 Dawes, E. A. and Senior, P. J. *Adv. Microb. Physiol.* 1973, **10**, 135
2 Byrom, D. *Trend. Biotechnol.* 1987, **5**, 246
3 Lusty, C. J. and Doudoroff, M. *Proc. Natl. Acad. Sci. U.S.A.* 1966, **56**, 960
4 Nakayama, K., Saito, T., Fukui, T., Shirakura, Y. and Tomita, K. *Biochim. Biophys. Acta* 1985, **827**, 63
5 Tanio, T., Fukui, T., Shirakura, Y., Saito, T., Tomita, K., Kaiho, T. and Masamune, S. *Eur. J. Biochem.* 1982, **124**, 71
6 Shirakura, Y., Fukui, T., Saito, T., Okamoto, Y., Narikawa, T., Koide, K., Tomita, K., Takemasa, T. and Masamune, S. *Biochim. Biophys. Acta* 1986, **880**, 46
7 Holmes, P. A. *Phys. Technol.* 1985, **124**, 71
8 Doi, Y., Tamaki, A., Kunioka, M. and Soga, K. *Appl. Microbiol. Biotechnol.* 1988, **28**, 330
9 Doi, Y., Kunioka, M., Nakamura, Y. and Soga, K. *Macromolecules* 1986, **19**, 2860
10 Doi, Y., Kunioka, M., Tamaki, A., Nakamura, Y. and Soga, K. *Makromol. Chem.* 1988, **189**, 1077
11 Bloembergen, S., Holden, D. A., Hamer, G. K., Bluhm, T. L. and Marchessault, R. H. *Macromolecules* 1986, **19**, 2865
12 Bluhm, T. L., Hamer, G. K., Marchessault, R. H., Fyfe, C. A. and Veregin, R. P. *Macromolecules* 1986, **19**, 2871
13 Mitomo, H., Barham, P. J. and Keller, A. *Polym. Commun.* 1988, **29**, 112
14 Kunioka, M., Nakamura, Y. and Doi, Y. *Polym. Commun.* 1988, **29**, 174
15 Doi, Y., Kunioka, M., Nakamura, Y. and Soga, K. *Macromolecules* 1988, **21**, 2722
16 Repaske, R. and Repaske, A. C. *Appl. Environ. Microbiol.* 1976, **32**, 585

Synthesis and thermogravimetric analyses of trisimides and polyimides derived from hexaazatriphenylene

K. Kanakarajan and Anthony W. Czarnik*

Department of Chemistry, The Ohio State University, Columbus, Ohio 43210, USA

(Received 14 October 1988, revised 22 November 1988)

The reaction of pyromellitic dianhydride with aminophenyl ether may be augmented by addition of hexaazatriphenylene trianhydride (**1**), a hydrogen-free, trifunctional copolymer. Even when the amount of **1** added as a crosslinking agent reaches 50 mol% of the total anhydride content, films can be cast and postcured thermally to provide polyimide films. As such, these results appear to run contrary to the prevailing wisdom, i.e. that more than a few per cent crosslinking will result in unprocessable 'brick dusts'. Thermogravimetric analyses of these novel crosslinked films reveal good thermal stabilities, although stability does decrease with increasing mole fractions of **1**.

(Keywords: polyimide; high temperature; crosslinked; hexaazatriphenylene; thermo-oxidative; film)

Introduction

The well-known reaction of aromatic dianhydrides with diamines yields polyamic acids, which are processable and can be postcured thermally to yield polyimides. Many polyimides afford excellent thermal stabilities, for example, one widely-used commercial polyimide, Dupont's Kapton, is stable to 500°C (isothermal) in N_2. Our research group recently discovered a simple synthesis of hexaazatriphenylene trianhydride (HAT-trianhydride, **1**) from commercially available starting materials. Because compound **1** is completely hydrogen-free, we felt it might prove useful as a crosslinking reagent in the synthesis of stable polyimide synthesis. This idea is predicated on the work of Hirsch[2] and of Vaughan[3], who demonstrated high thermo-oxidative stability in polyimides completely devoid of hydrogen. Therefore, in order to determine how HAT-induced crosslinking of the pyromellitic dianhydride-aminophenyl ether polyimide influenced its thermal stability, we have prepared polyimides containing varying amounts of added trianhydride **1** (ref. 5): See *Scheme*.

Experimental

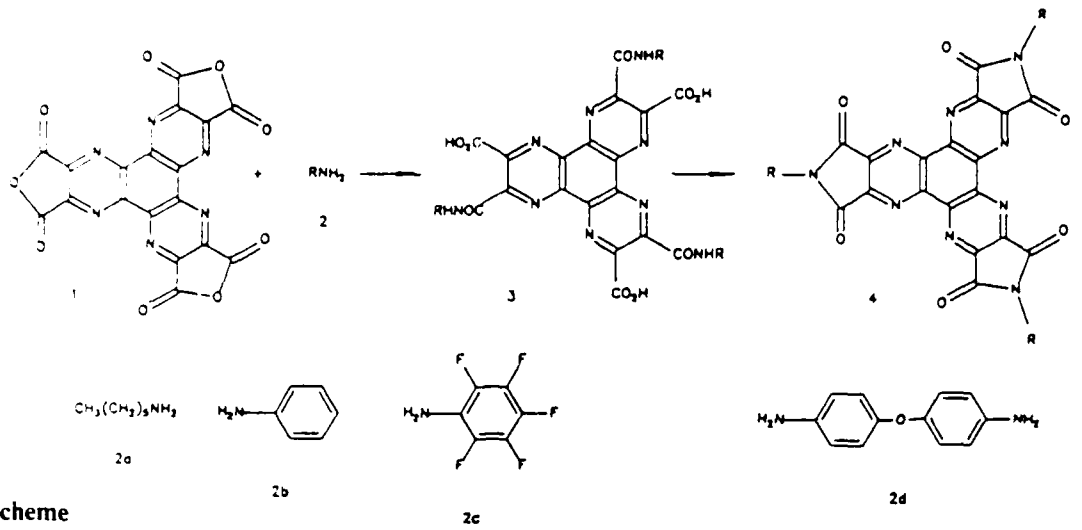
Mass spectra were obtained by use of a Kratos-30 mass spectrometer. *FT*n.m.r. spectra at 11.75 tesla (500 MHz) or 7.0 tesla (300 MHz) were obtained using equipment funded in part by NIH Grant No. 1 S10 RR01458-01A1. Thermogravimetric analyses (t.g.a.s) were performed on a Dupont Model 9900 Thermal Gravimetric Analyser in either air or argon. The t.g.a. results depicted in *Figures 1* and *2* show continuous curves obtained by graphical smoothing of the rough data.

HAT-trianhydride (**1**) was prepared from the corresponding hexanitrile as described previously[1].

Monomeric triimides (**4a–4c**) were prepared by reaction of compound **1** with an excess of the appropriate

* To whom correspondence should be addressed

0263 6476/89/060171 03$03.00



Scheme

desired amine (**2a–2c**) followed by chemical imidization as we have described more fully elsewhere[4]. In the course of our synthetic efforts, we found that the use of trifluoroacetic anhydride in place of acetic anhydride often leads to cleaner imidization products. The synthesis of the tri-*N*-phenyltrisimide (**4b**) exemplifies the general method used.

Synthesis of tri(N-phenyl)-1,4,5,8,9,12-hexaazatriphenylene-2,3,6,7,10,11-hexacarboxylic acid trisimide **4b**. Trianhydride **1**, prepared as described above from the hexaacid (500 mg, 1 mmol), was dissolved in dry dimethylacetamide (15 ml) and treated with freshly distilled aniline (1.5 g). The mixture was heated on a steam bath for 15 min, cooled, poured onto ice (35 g), and acidified with concentrated HCl (15 ml). The resulting solid was filtered, washed with water, and dried *in vacuo* at room temperature to give triamic acid **3b** (550 mg, 74%), m.p. 198–203 C. The crude triamic acid (550 mg, 0.76 mmol) was mixed with trifluoracetic anhydride (5 ml) and trifluoroacetic acid (0.3 ml) and heated in a sealed tube on a steam bath for 48 h. The reaction was evaporated to dryness and the residue was recrystallized/precipitated from ethyl acetate toluene to afford trisimide **4b** (505 mg, 75%), m.p. > 290°C; u.v. (DMSO): 282, 320 nm; ^{13}C n.m.r. (DMSO-d_6): 127.1, 128.9, 129.2, 131.2 (phenyl carbons), 144.6 (internal aromatic carbons), 148.6 (peripheral aromatic carbons), 163.0 (carbonyl carbons) ppm; fast atom bombardment mass spectrum: m e 672 ($M^+ + 3$).

Polymerization reactions leading to polyamic acids were conducted in DMAc and were carried out in the usual way. After gelling for 1 h, the solution was spread over a glass plate and heated at 60°C for 10 h to provide the polyamic acid film. Imidization of the polyamic acid could be accomplished by heating in an oven at 4°C min^{-1} to 350°C, followed by continued heating at 350°C for an additional 45 min. However, in order to establish imidization temperatures, t.g.a. analyses were conducted on powder samples of the polyamic acids. Such powder samples were obtained by adding the gelled DMAc solution dropwise to a large excess of diethyl ether, followed by collection of the resulting solid by filtration and air drying.

Results and discussion

We were able to prepare trisimides **4a–4c** in good yield as models for polyimides derived from trianhydride **1**. The ^{13}C n.m.r. spectra of these trisimides reveal a high degree of symmetry as expected for compounds with D_{3h} symmetry. For example, the ^{13}C n.m.r. spectrum of **4a** demonstrates only three lines for aromatic and or carbonyl carbons and six lines for aliphatic carbons (9 lines total) even though the compound itself contains 36 carbons. T.g.a.s of these trisimides are shown in *Figure 1*. Although the crystalline hexyl derivative **4a** is obtained in purer form than are the two noncrystalline trisimides examined, it seems apparent that both phenyl- (**4b**) and pentafluorophenyl (**4c**) monomeric trisimides are themselves quite stable materials. The thermal decomposition temperature of **4a** is fully 100°C lower than that of **4b**, consistent with the expected thermal instability of the alkyl groups in **4a**. Contrary to expectation, the perfluoro substitution in **4c** decreased rather than increased the thermal stability of that model trisimide.

Having demonstrated the relative stability of the HAT crosslinking units, we prepared a series of modified Kapton polymers in order to evaluate the effect of HAT-induced crosslinking on polymer decomposition temperatures. The high reactivity of the anhydride groups in **1** (ref. 4) as compared to those in pyromellitic dianhydride (PMDA) guarantees that all three sites in **1** will react with **2d**, thereby inducing crosslinks into the matrix. Polyamic acids were made between PMDA and **2d** in which from 0–50 mol% of the anhydride equivalents

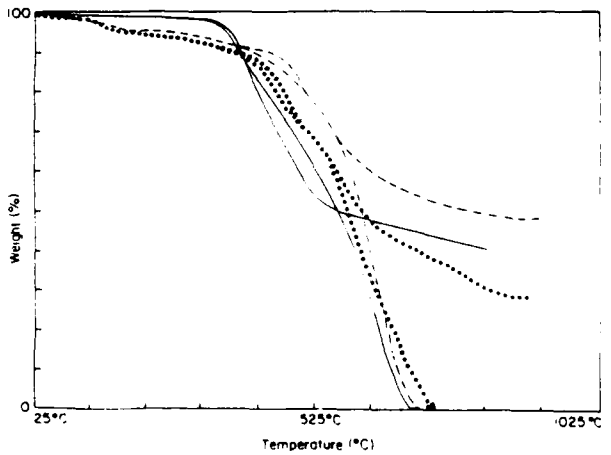


Figure 1 T.g.a. of trisimides **4a** (———), **4b** (- - - -) and **4c** (· · · ·) in argon (upper three traces) and in air (lower three traces)

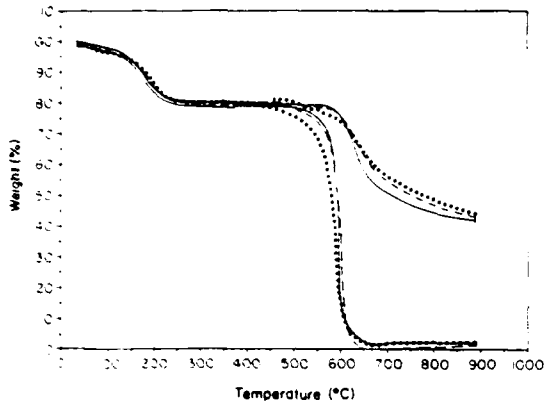


Figure 2 T.g.a. of Kapton polyamic acids incorporating trianhydride **1** to 0 mol%, (——), 10 mol%, (-----) and 50 mol% (·····) in argon (upper three traces) and in air (lower three traces)

were replaced by HAT-trianhydride (**1**), and powdered samples were obtained by precipitation of the DMAc solution with ether. T.g.a. analyses were determined on the polyamic acids in order to measure the thermal imidization temperatures of the modified polymers. These t.g.a. results are shown in *Figure 2*, from which two conclusions can be drawn: first, the temperature range for thermal imidization (*ca.* 150–225°C) is unchanged by addition of HAT-trianhydride; and second the thermal stability of 50% HAT-modified Kapton polyimides is less than that of unmodified Kapton, while that of 10%-modified is only slightly less than that of Kapton.

The most striking observation made during the course of this work concerns the ability of HAT-crosslinked polyimides to form films. We had expected that the addition of only a few per cent of the crosslinking reagent would lead to insoluble powders incapable of being cast into films. Instead, polyamic acid films could be made with 0, 5, 10, 15, 20 and 50 mol% **1**; each could further be thermally imidized to provide polyimide films. The polyamic acid obtained between aminophenyl ether and **1** with no added PMDA remained in solution, but the resulting film could not be peeled off the glass plate cleanly. The colour of polyamic acid film samples changed progressively from yellow (0%) to orange (10%) to red orange (20%) to red (100%) as the mol% of HAT-trianhydride increased. This colour change is consistent with the charge-transfer (CT) explanation for the yellow colour of Kapton, given our experience that HAT derivatives are strongly electron-deficient compounds capable of forming CT complexes with a variety of electron-rich aromatic molecules.

Conclusion

We have observed that film casting of even highly crosslinked solutions of HAT-modified polyimides is possible, a finding that is contrary to the prevailing notion of the effect of extensive crosslinking on polymer processability. While the trend in stability is not what we had anticipated, it was nonetheless encouraging that even the most highly enriched film exhibited good thermal stability; we anticipate that small incorporations of **1** will affect stability less. As a result, we are examining the synthesis of monosubstituted derivatives of **1** that can be incorporated into polyimides, deprotected and finally activated to provide sites on the polymer that can be functionalized prior to thermal curing.

Acknowledgement

We thank Dr Stanley Wentworth for both helpful advice during the course of this work and assistance in obtaining t.g.a.s on our samples. We thank Mr Richard Weisenberger and Dr C. E. Cottrell for their assistance in obtaining mass and high-field ^{13}C n.m.r. spectra, respectively, at The Ohio State University Chemical Instrumentation Center and Mr Carl Engelman for other n.m.r. assistance. This work was funded by the Army Research Office and the US Army Materials Technology Laboratory.

References

1 Kanakarajan, K. and Czarnik, A. W. *J. Org. Chem.* 1986, **51**, 5241
2 Hirsch, S. S. *J. Polym. Sci., Polym. Chem. Edn.* 1969, **7**, 15
3 Vaughan, G. B., Rose, J. C. and Brown, G. P. *J. Polym. Sci., Pt. A-1* 1971, **9**, 1117
4 Kanakarajan, K. and Czarnik, A. W. *J. Heterocycl. Chem* 1988, **25**, 1869
5 Kanakarajan, K. and Czarnik, A. W. *Soc. Adv. Mater. Process Eng. Ser.* 1988, **33**, 956; *Polym. Prepr.* 1988, **29**, No. 1, 246

Application of extrapolation procedures to viscosity data below the theta temperature

J. S. Lindner*
Diagnostic Instrumentation and Analysis Laboratory, Mississippi State University, Mississippi State, Mississippi 39762, USA

N. Hadjichristidis
Department of Chemistry, University of Athens, Athens (106 80), Greece

and J. W. Mays
Department of Chemistry, University of Alabama at Birmingham, Birmingham, Alabama 35294, USA
(Received 29 August 1988; revised 7 November 1988)

Intrinsic viscosities are reported for poly(α-methylstyrene) in cyclohexane from very near the θ temperature (36.2 C) to about 16 C below θ. Six near-monodisperse samples covering the range 5.9×10^4 g mol$^{-1} \leqslant \bar{M}_w \leqslant 1.14 \times 10^6$ g mol^{-1} were used for this purpose. Over the investigated range of temperature the Mark–Houwink–Sakurada exponent decreased from 0.498 to 0.386. No signs of aggregation were observed. Various extrapolation procedures, originally advanced for the determination of unperturbed dimensions from viscosity data in moderate and good solvents, were applied to the data. Results indicate that values of K_θ can be accurately determined from viscosity data below θ.

(Keywords: poly(α-methylstyrene) in cyclohexane; intrinsic viscosity; extrapolation; sub-theta temperature)

Introduction

A number of extrapolation procedures have been advanced[1-7] for estimating unperturbed dimensions of flexible polymers from intrinsic viscosity measurements in moderate and good solvents, i.e. above the Flory θ temperature. In particular, the Burchard–Stockmayer–Fixman (B–S–F) method[1,2] has yielded reliable estimates of unperturbed dimensions for a wide variety of chains, especially when the exponent of the Mark–Houwink–Sakurada (M–H–S) expression:

$$[\eta] = KM^a \tag{1}$$

is less than 0.7 and molecular weights are above a few thousand and less than about 1×10^6 g mol^{-1} (reference 8). The B–S–F relationship is given as:

$$[\eta] = K_\theta M^{1/2} + 0.51\phi_0 BM \tag{2}$$

where $[\eta]$ is the limiting viscosity number, $K_\theta = [\eta]_\theta / M^{1/2}$ and the subscript θ denotes the state where the second virial coefficient, A_2, equals zero. The parameter ϕ_0 is a universal constant for flexible linear near-monodisperse chains under θ conditions and B is related to the binary cluster integral, β. Equation (2) suggests that a plot of $[\eta] M^{1/2}$ against $M^{1/2}$ will yield K_θ as the intercept with B obtained from the slope.

Other expressions have been derived based on relationships for the dependence of the expansion factors for viscosity, $\alpha_\eta^3 = [\eta]/[\eta]_\theta$, and radius of gyration $\alpha_s = \langle s^2 \rangle^{1/2} / \langle s^2 \rangle_\theta^{1/2}$ for the r.m.s. end-to-end distance R^2) on the quantity Z of two-parameter theory. Early work by Kurata and Stockmayer[3] yielded

$$[\eta]^{2/3} M^{1/3} = K_\theta^{2/3} + 0.363\phi_0 B g(\alpha_\eta) M^{2/3} [\eta]^{1/3} \tag{3}$$

where

$$g(\alpha_\eta) = 8\alpha_\eta^3 / (3\alpha_\eta^2 + 1)^{3/2}$$

The perturbation theory of Yamakawa and Tanaka[9] resulted in a modified B–S–F expression

$$[\eta]/M^{1/2} = K_\theta^{1/2} + 0.35\phi_0 BM^{1/2} \tag{4}$$

while Berry[4], empirically suggested

$$[\eta]^{1/2}/M^{1/4} = K_\theta^{1/2} + 0.42K_\theta^{1/2}\phi_0 BM/[\eta] \tag{5}$$

Equations (2), (3) and (4) have been reviewed for viscosity results in good solvents[5].

In addition to the above equations Tanaka[6], using a Padé approximation, has proposed:

$$([\eta]/M^{1/2})^{5/3} = K_\theta^{5/3} + 0.667\phi_0^{5/3}(\langle R^2 \rangle_0 / M)BM^{1/2} \tag{6}$$

This expression was shown by Stickler *et al.*[10] to lead to linear plots using data obtained above the θ point.

An alternate approach for the determination of K_θ was given by Kamide and Moore[7]. This method uses values of K and a from equation (1) according to

$$-\ln K + \ln\{2[(a - 1/2)^{-1} - 2]^{-1} + 1\} = \alpha - 1.2 \ln M_0 - \ln K_\theta \tag{7}$$

where M_0 is the appropriate molecular weight average, i.e. $\bar{M}_v$ or $\bar{M}_w$, employed in evaluation of the M–H–S relation.

In this work, we assessed the validity of the above approaches for estimating unperturbed dimensions from viscosity data obtained under very poor solvent conditions (from $T = \theta = 36.2$–20 C). A series of near-monodisperse poly(α-methylstyrenes) (PαMS) were employed for this purpose. PαMS is particularly well-suited to a study of this type since it has been noted[11,12] that even high molecular weight samples ($M_w = 1 \times 10^6$ g mol^{-1}) remain in solution well below the θ temperature and the temperature coefficient of chain dimensions is known to be nearly zero[12]. In all cases we concentrate on the parameter K_θ. Although values of B

* To whom correspondence should be addressed

0263 6476/89/060174-03$03.00

Reprinted from The Journal of Organic Chemistry, 1986, Vol. 51, page 5241

Synthesis and Some Reactions of Hexaazatriphenylenehexacarbonitrile, a Hydrogen-Free Polyfunctional Heterocycle with D_{3h} Symmetry

K. Kanakarajan and Anthony W. Czarnik*

Department of Chemistry, The Ohio State University, Columbus, Ohio 43210

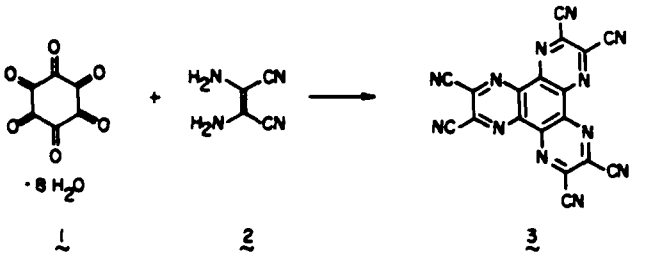
Received June 16, 1986

In this paper, we report for the first time the synthesis of hexaazatriphenylenehexacarbonitrile, abbreviated HAT-hexacarbonitrile. This hydrogenless, symmetrically branched compound can be prepared in analytically pure form on a large scale by using commercially available starting materials. The conversions of HAT-hexacarbonitrile to the corresponding hexaamide, hexaacid, hexaester, and trianhydride derivatives were also accomplished.

In this paper we report the first synthesis of hexaazatriphenylenehexacarbonitrile (HAT-hexacarbonitrile) (3) by a simple method from readily available precursors. Derivatives of this compound, containing no hydrogen, are potentially useful in the preparation of thermally stable, oxidation-resistant polymers.[1] Hexaazatriphenylene (HAT-H_6) itself has been made previously, but the first reported sequence[2] is rather long and does not suggest an easy way to incorporate the kind of multiple functionality present in hexacarbonitrile 3. Recent methods using hexaaminobenzene[3] as the starting material are shorter, but have been utilized preparatively only in the syntheses of hexaalkyl-HAT's[3a] and, more recently, HAT-H_6 itself.[3b] Therefore, we now describe the one-step synthesis of hexacarbonitrile 3 and its conversion to hexaamide 4, hexaacid 5, hexaester, and trianhydride 6 derivatives.

Our starting material, hexaketocyclohexane octahydrate (1), is available commercially but is rather expensive. We have therefore prepared it in a two-step reaction from glyoxal; self-condensation to afford tetrahydroxyquinone proceeds as described previously,[4] and then oxidation to compound 1 was accomplished by using a modified literature[5] method. Reaction of hexaketone 1 with an excess of diaminomaleonitrile (2) in refluxing glacial acetic acid affords hexacarbonitrile 3 in 81% yield as shown in Scheme I. Our procedure is in close analogy to that used by Skujins and Webb in their condensation of hexaketone 1 with *o*-phenylenediamine.[6] Hexacarbonitrile 3 is isolated by simple filtration from the hot reaction mixture and is analytically pure after drying. Its ^{13}C NMR spectrum reveals the simple pattern expected for a compound with D_{3h} symmetry, and we observe three singlets: one for nitrile carbons, one for peripheral aromatic carbons, and one for internal aromatic carbons. As anticipated, the compound is quite insoluble in nonpolar organic solvents, but solutions in DMF or Me_2SO can be made. A DMF solution with tetrabutylammonium perchlorate as the supporting electrolyte was used to establish a chemically reversible couple centered at −0.105 V (ΔE_p 100 mV) vs. aqueous SCE (−0.595 V vs. ferrocene) for compound 3 leading to its radical anion; a second, irreversible couple leading to the dianion was observed at −0.495 V.

Scheme I



1 2 3

Hydration of hexacarbonitrile 3 to hexaamide 4 is accomplished readily using concentrated sulfuric acid at room temperature for 3 days (Scheme II). As in every reaction involving derivatives of 3, it is particularly important that *all* of the functional groups be converted to the next in very high yield; a procedure that afforded the pentacarboxamide mononitrile as a contaminant, for example, would be useless. ^{13}C NMR of hexaamide 4 again reveals the simple pattern expected, except that the peripheral carbons are coupled to one of the amide NH's.[7] Coupling to only *one* of the two amide NH's can be rationalized by recalling that $J_{C,H}$ experiences the same kind of angular dependence that $J_{H,H}$ does.[8] The approximately 7-Hz coupling constant we measure is consistent with long-range C–H coupling, and only the amide NH syn to the carbonyl oxygen exists in a "w conformation" with respect to the peripheral carbon; we propose, therefore, that it is the only proton coupling to that carbon. Of special interest is the ability of laser desorption Fourier transform ion cyclotron resonance mass spectrometry[9] to yield a molecular ion for this highly polar, nonvolatile molecule (K^+ complex ion observed). No other mass spectrometric technique we have tried gave us any interpretable data on this compound.

Attempted basic hydrolyses ($NaOH/H_2O$/heat or Na_2O_2/H_2O) of hexaamide 4 to hexaacid 5 consistently yielded mixtures of partially hydrolyzed polyacids, determined by ion-exchange chromatography and by paper electrophoresis; this result is not too surprising, as hydroxide attack is expected to become progressively slower on the progressively greater charged polyacid. Acidic hydrolysis methods also gave mixtures of insoluble products that were not readily characterized. We were suc-

(1) For introductory reading, see: (a) Labana, S. S., Ed. *Chemistry and Properties of Crosslinked Polymers*; Academic: New York, 1977; pp 85–137. (b) Frazier, A. H., *High Temperature Resistant Polymers*; Wiley: New York, 1698; pp 285–318.

(2) Nasielski-Hinkens, R.; Benedek-Vamos, M.; Maetens, D.; Nasielski, J. *J. Organomet. Chem.* **1981**, *217*, 179.

(3) (a) Kohne, B.; Praefcke, K. *Liebigs Ann. Chem.* **1985**, 522. (b) Rogers, D. Z. *J. Org. Chem.* **1986**, *51*, 3904 (this paper describes both a convenient synthesis of hexaaminobenzene and its conversion to hexaazatriphenylene with glyoxal in 83% crude yield).

(4) Fatiadi, A. J.; Sager, W. F. *Organic Syntheses*; Wiley: New York, Collect. Vol. V, p 1011.

(5) (a) Nietzki, R.; Benckiser, T. *Ber.* **1885**, *18*, 506. (b) Ochiai, E.; Kobayashi, Y.; Haginiwa, T.; Takeuchi, S.; Fujimoto, M. *Chem. Abstr.* **1967**, *66*, 104832.

(6) Skujins, S.; Webb, G. A. *Tetrahedron* **1969**, *25*, 3935.

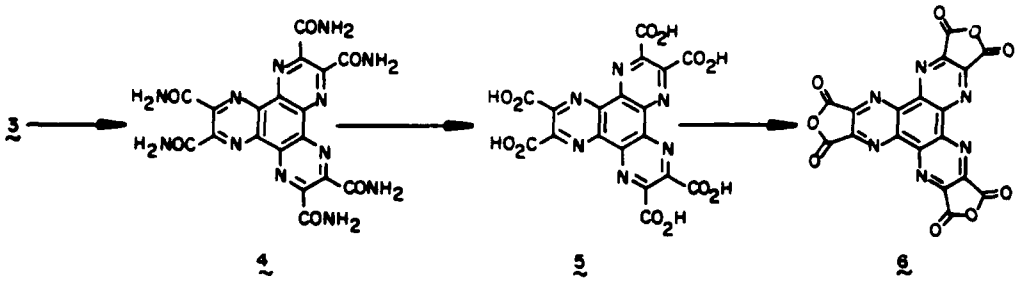
(7) It is not surprising that the carbonyl carbon does not couple to the adjacent amide proton; the almost complete lack of carbonyl coupling to adjacent (but not directly bonded) protons allowed early ^{13}C NMR investigators to observe signals before the advent of decoupling methods.

(8) Wiberg, K. B.; Lampman, G. M.; Civia, R. P.; Connor, D. S.; Schertler, P.; Lavanish, J. *Tetrahedron* **1965**, *21*, 2749.

(9) Marshall, A. G. *Acc. Chem. Res.* **1985**, *18*, 316.

0022-3263/86/1951-5241$01.50/0

Scheme II



cessful in converting hexaamide to hexaacid under diazotizing conditions[10] by using sodium nitrite in trifluoroacetic acid, and precipitation of the sodium salt afforded the hexacarboxylate as confirmed by its microanalysis and simple ^{13}C NMR spectrum taken in D_2O/H_2O. As compared to the highly water-insoluble hexacarbonitrile or hexaamide, hexaacid 5 is very water soluble as its polycarboxylate. Vigorous treatment with HCl results in ion exchange and precipitation of the less soluble carboxylic acid form with no observable decarboxylation; acid-catalyzed esterification with methanol yields the hexamethyl ester in 84% yield. In addition, the hexaacid forms water-insoluble metal ion complexes; this work is still in progress and will be reported at a later date.

Trianhydride formation was accomplished by using hot acetic anhydride by analogy to the known[11] conversion of pyrazine-2,3,5,6-tetracarboxylic acid to the corresponding dianhydride. Temperature control seems particularly important in our conversion, as does starting with a sample of the hexaacid that has been completely converted to the H^+ form. We find that heating a suspension of hexaacid 5 in freshly distilled acetic anhydride at 114–116 °C for 10 min yields a homogeneous solution that, upon evaporation, gives the trianhydride 6 as a moisture-sensitive solid. Crystallization from acetonitrile/benzene/trifluoroacetic anhydride affords a crystalline, moisture-sensitive solid whose ^{13}C NMR spectrum consists of three lines. Treatment of the ^{13}C NMR sample with 1 equiv of H_2O led to a significantly complicated spectrum that, upon further addition of excess H_2O, again demonstrated a three-line spectrum identical with that of the hexaacid in the same solvent. The trianhydride is much more soluble in organic solvents (e.g., acetonitrile) than the other HAT derivatives we have prepared.

In summary, we have reported a one-step tricondensation reaction that leads to the hexaazatriphenylene nucleus in excellent yield. Manipulation of the functionality available on HAT-hexacarbonitrile will lead to derivatives heretofore unavailable, such as the three we have described in this paper. We expect to report on the synthetic methods required, as well as studies on the physical properties of these compounds, as our work in this area continues.

Experimental Section

General. Melting points were taken on an Electrothermal melting point apparatus and are uncorrected. Microanalyses were carried out at Canadian Microanalytical Service, New Westminster, B.C. Mass spectra were obtained by use of a Kratos-30 mass spectrometer. FT-NMR spectra at 11.75 (500 MHz) or 7.0 T (300 MHz) were obtained with equipment funded in part by NIH Grant 1 S10 RR01458-01A1. We thank Richard Weisenberger and Dr. C. E. Cottrell for their assistance in obtaining mass and high-field ^1H NMR spectra, respectively, at The Ohio State University Chemical Instrumentation Center, and Carl Engelman for other NMR assistance.

Hexaketocyclohexane Octahydrate (1). We have modified the original procedure reported by Nietzki et al.[5a] as follows: Powdered sodium tetrahydroxyquinone[4] (10.8 g, 50 mmol) was added in portions to a stirred, ambient temperature solution of 25% HNO_3 (150 mL) over a period of 10 min. The temperature of the vigorous reaction was controlled at 45 ± 5 °C by using an ice bath, and the resulting clear, light yellow solution was cooled at 5 °C. Colorless crystals formed and were collected by filtration, washed with cold water (3 × 30 mL), and dried to give 1 (11.7 g, 80%): mp 95–96 °C dec (lit.[5b] mp 95–96 °C dec).

Hexaazatriphenylenehexacarbonitrile (3). A mixture of hexaketocyclohexane octahydrate (10.0 g, 32 mmol) and diaminomaleonitrile (26.0 g, 240 mmol) in glacial acetic acid (1200 mL) was heated to reflux with stirring for 2 h. The black reaction was filtered hot, and the solid was washed with hot glacial acetic acid (3 × 150 mL). Drying over KOH pellets at 150 °C and 0.01 torr for 2 h afforded a brown-black[13] solid (10.1 g, 81%): mp >350 °C; ^{13}C NMR ($(CD_3)_2SO$) δ 114.2 (br s, CN's), 135.4 (s, internal Ar carbons), 141.6 (s, peripheral Ar carbons); IR (KBr pellet) 2250 cm^{-1} (weak, CN); UV (Me_2SO) 288 nm, 310; desorption chemical ionization mass spectrum (CH_4), m/e (relative intensity) 385 (100, $[M + 1]^+$).

Anal. Calcd for $C_{18}N_{12}$: C, 56.25; H, O; N, 43.75. Found: C, 56.09; H, 0.14; N, 43.60.

Hexaazatriphenylenehexacarboxamide (4). A solution of HAT-hexacarbonitrile (4.80 g, 12.5 mmol) in concentrated H_2SO_4 (100 mL) was stirred at room temperature for 72 h and then was added dropwise to rapidly stirred ice–water (3 L). The solid was collected by filtration, washed with water (3 × 100 mL) and acetone (3 × 100 mL), and dried at 100 °C and 0.01 torr for 14 h to provide a gray-black solid (5.38 g, 87%): mp >350 °C; ^{13}C NMR ($(CD_3)_2SO$) δ 140.5 (s, internal Ar carbons), 148.3 (d, J = 7.3 Hz, coalesces to s with broad-band ^1H decoupling, peripheral Ar carbons), 166.2 (s, $CONH_2$'s); IR (KBr pellet) 1680 cm^{-1} (strong, C=O); UV (Me_2SO) 280 nm, 322; laser desorption FT ICR mass spectrum; m/e (relative intensity) 531 (100, $[M + K]^+$).

Anal. Calcd for $C_{18}H_{12}N_{12}O_6 \cdot H_2O$: C, 42.35; H, 2.77; N, 32.94. Found: C, 42.62; H, 2.74; N, 33.00.

Hexaazatriphenylenehexacarboxylic Acid (5). A solution of HAT-hexacarboxamide (4.92 g, 10 mmol; 4) in trifluoroacetic acid (150 mL) was stirred at room temperature. Solid sodium nitrite (7.0 g, 90 mmol) was added to this solution portionwise over a period of 15 min, with the temperature kept under 25 °C by cooling with an ice bath. An initial brisk evolution of gas was noted, and the black solution changed to an orange brown suspension. Acetic acid (150 mL) was added, the mixture was stirred

(10) Andenheim, H.; Bender, M. L. *J. Am. Chem. Soc.* **1966**, *82*, 1896.
(11) Hirsch, S. S. *J. Polym. Sci.* **1969**, *7*, 15.
(12) While the ^{13}C NMR spectrum of this compound clearly demonstrates its structure as the trianhydride, its high reactivity with water has frustrated our efforts at microanalysis. Even with desiccated shipping methods, this compound analyzed correctly for $C_{18}N_6O_6$ plus 0.6 molecules of H_2O, indicating partial hydrolysis.
(13) One reviewer has suggested that this color is due to an impurity of the phthalocyanine self-condensation product of nitrile 3, which could form during the initial acetic acid reaction. In our experience, the only way to check the purity of this compound is to take its ^{13}C NMR spectrum. The Me_2SO-d_6 solution used must be stirred for several hours at room temperature to ensure complete dissolution. Samples that are either (a) impure because of defective starting materials or improper reaction conditions or (b) incompletely dissolved will demonstrate very broad singlets even for the aromatic carbons. We now routinely test every batch of HAT-hexacarbonitrile in this way before its further conversion.

for 12 h and poured into ice–water (300 mL), and the crude product was collected by filtration. The solid was dissolved in sodium bicarbonate solution (20 g in 150 mL water) and filtered to remove any insoluble solid. The filtrate was treated with activated charcoal, heated to boiling, and filtered to give a clear yellow solution that was treated with a cold sodium hydroxide solution (20.0 g in 100 mL water). An immediate precipitation of sodium HAT-hexacarboxylate as a yellow solid occurred, and complete precipitation of the salt was effected by the addition of ethanol (30 mL). The product was filtered, washed with 50% aqueous alcohol (3 × 50 mL), and dried under vacuum [100 °C (0.1 torr)] to afford 4.53 g of the polysodium salt of **5**: IR (KBr pellet) μ 1618 cm^{-1} (>C=O); ^{13}C NMR (D_2O/H_2O) δ 140.00 (s, internal carbons), 151.08 (s, peripheral carbons), 171.70 (s, carboxylate carbons).

The **free acid** was obtained as follows: Polysodium HAT-hexacarboxylate (2.52 g, 40 mmol) was suspended in water (100 mL), heated to 50 °C, and acidified by adding concentrated HCl (100 mL). The mixture that formed was heated at 90 °C for 1 h, then was filtered, washed with 10% HCl (3 × 25 mL), and finally washed with deionized water 2 × 25 mL). The product was dried at 120 °C (0.1 torr) to give **5** (1.88 g, 89.5%) as its sesquihydrate: mp >350 °C; ^{13}C NMR (D_2O/dilute NH_4OH) δ 140.1 (s, internal Ar carbons), 151.2 (s, peripheral Ar carbons), 171.7 (s, carboxyl carbons); IR (KBr pellet) μ 1730 cm^{-1} (>C=O); UV (Me_2SO) 278 nm, 316.

Anal. Calcd for $C_{18}H_6N_6O_{17}$·1.5H_2O: C, 41.16; H, 1.73; N, 15.99. Found: C, 41.07; H, 1.91; N, 15.82.

The **hexamethyl ester** was prepared as follows: A solution of hexaacid acid **5** (525 mg of the sesquihydrate, 1 mmol) in absolute methanol (200 mL) and concentrated sulfuric acid (1 mL) was heated to reflux with stirring for 10 h. The solid was collected by filtration, washed with aqueous methanol (50 mL), and dried at 100 °C and 0.01 torr for 6 h to provide a cream colored solid (490 mg, 84%) that could be recrystallized from acetonitrile: mp >350 °C; ^{13}C NMR (Me_2SO-d_6) δ 164.02 (s, ester carbonyl carbons), 145.08 (s, internal or peripheral Ar carbons), 142.23 (s, internal or peripheral Ar carbons), 53.63 (s, methyl carbons); ^1H NMR ($CDCl_3/CF_3COOH$) δ 4.17 (s, CH_3); IR (KBr pellet) μ 1750 cm^{-1} (strong, C=O); UV (Me_2SO) 274 nm, 312; FAB mass spectrum, m/e 583 ($M^+ + 1$).

Anal. Calcd for $C_{24}H_{18}N_6O_{12}$: C, 49.48; H, 3.09; N, 14.43. Found: C, 49.12; H, 3.14; N, 14.50.

Hexaazatriphenylenehexacarboxylic Acid Trianhydride (6). HAT-hexacarboxylic acid (1.25 g, 23.8 mmol; **5**) was added to freshly distilled acetic anhydride (60 mL) and heated to 115 ± 2 °C under a nitrogen atmosphere. The vigorously stirred mixture turned to a clear brown solution within 10 min, then heating was discontinued, and the solution was allowed to cool over a period of 20 min. The solvent was removed by rotary evaporation under reduced pressure, and the residue was recrystallized from acetonitrile and benzene (by using a few drops of trifluoroacetic anhydride as desiccant) to give **6** (963 mg, 95%) as moisture-sensitive needles: mp >350 °C; ^{13}C NMR (CD_3CN) δ 159.58 (s, carbonyl carbons), 148.62 (s, internal or peripheral Ar carbons), 148.15 (s, internal or peripheral Ar carbons); IR (KBr) μ 1820 (strong), 1880 cm^{-1} (>C=O).

Anal.[12] Calcd for $C_{18}N_6O_9$·0.6 H_2O: C, 47.51; H, 0.27; N; 18.47. Found: C, 47.88; H, 0.30; N, 18.11.

Acknowledgment. We appreciate the efforts of Sheila Schutte in performing the cyclic voltametry experiments described in this paper; in addition, we are grateful to Dr. Alan Schwalbacher and Prof. Przemyslaw Maslak who made timely suggestions and to Dr. Stanley Wentworth for both helpful discussions and shared interest in this work. The assistance of Ron Shomo in conducting the mass spectrometry experiment of hexaamide **4** and of Dr. M. S. P. Sarma in preparing hexaketocyclohexane octahydrate is acknowledged. Initial funding for this work via a starter grant from the American Cancer Society—Ohio Division and subsequent major funding from the Army Research Office is acknowledged with gratitude.

Syntheses of Some Hexacarboxylic Acid Derivatives of Hexaazatriphenylene

K. Kanakarajan and Anthony W. Czarnik*

Department of Chemistry, The Ohio State University, Columbus, Ohio 43210

Received May 16, 1988

Synthetic methods and product characterizations for the conversions of 1,4,5,8,9,12-hexaazatriphenylenehexacarboxylic acid to the corresponding triester triacid, triamic acid, triimide, triester triacid chloride, trimethyl triethyl hexaester, trimethyl ester tri(*N,N*-dimethyl)amide, hexaamide, tri(*N,N*-dimethyl)amide triacid, tri(*N,N*-dimethyl)amide triacid chloride, and trisphthalhydrazide derivatives are described.

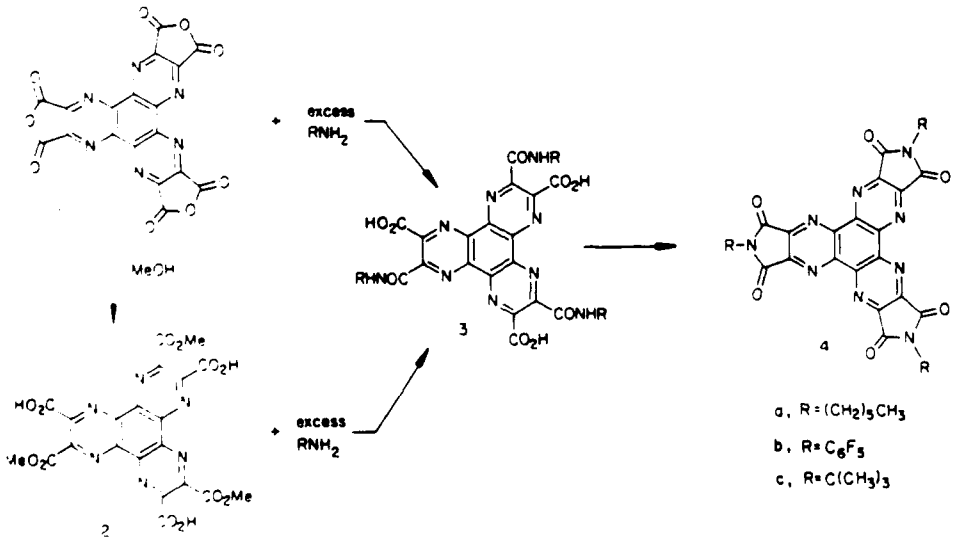
J. Heterocyclic Chem., **25**, 1869 (1988).

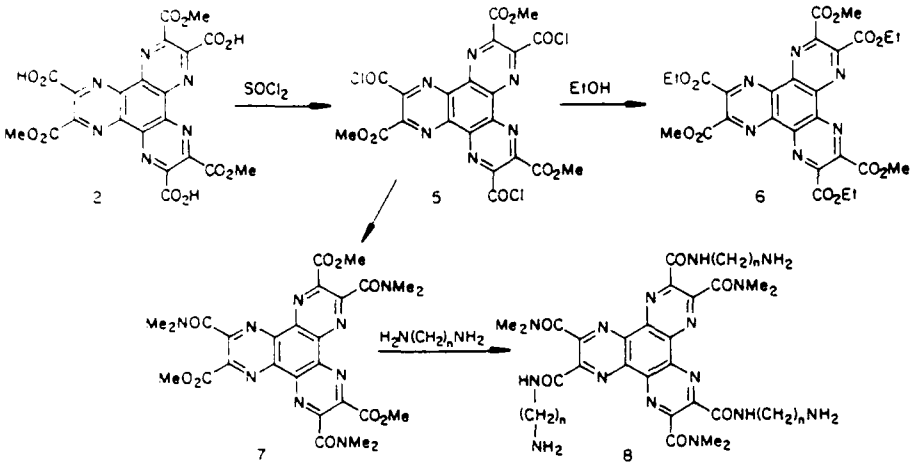
As part of our interest in the use of hexaazatriphenylene (HAT) derivatives for the synthesis of thermooxidatively-stable polymers [1], we have been studying the chemistry of hexaazatriphenylene trianhydride (**1**). In this report, we focus on the synthesis of hexasubstituted derivatives of HAT useful for the preparation of polyimides [2], *i.e.*, all substituents at the carboxylic acid oxidation level.

Hexaazatriphenylene trianhydride (**1**) proved to be an unusually reactive aromatic anhydride. While it can be obtained in crystalline form [3], reaction with atmospheric moisture is extremely facile; for this reason, it is not convenient to store the anhydride. As one solution, we reacted anhydride **1** immediately with anhydrous methanol to afford the triester triacid **2**, which is a solid and infinitely stable when stored in a desiccator. Two isomeric triester triacids are possible in this reaction: compound **2**, which possesses D_{3h} symmetry, and the unsymmetrical derivative in which one set of ester and acid groups has been interchanged. To the limits of our analytical detection (*ca.* 5% by ^{1}H nmr), only the symmetrical isomer **2** is obtained in this reaction, based on the simplicity of the ^{1}H and ^{13}C nmr spectra obtained. Of course, this conclusion is based on an imperfect assumption that the two isomers would not have superimposible spectra.

Both trianhydride **1** and triester triacid **2** can be reacted with primary amines to provide symmetrical amic acids **3**, although the trianhydride route is preferable with relatively unreactive amines (*e.g.*, *t*-butylamine). The amic acids can be conveniently isolated by acid-precipitation from aqueous solution. Chemical imidization (*i.e.*, **3** → **4**) was accomplished using a variety of dehydrating agents, including acetic anhydride, trifluoroacetic anhydride, and thionyl chloride. The resulting triimides **4a-c** were high-melting solids, whose ^{13}C nmr spectra revealed the simple patterns expected for symmetrical compounds [4].

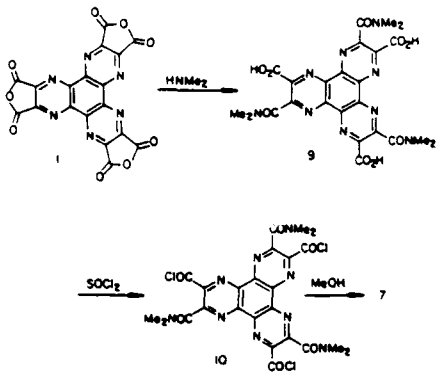
The preparation of triamic acids derived from α,ω-diamines led to zwitterionic products with unacceptable solubility properties. For example, the reaction of trianhydride **1** with 1,6-hexanediamine provides compound **3**, R = $(CH_2)_6NH_2$, that is soluble in water but highly insoluble in methanol, chloroform, THF, DMF, dimethylacetamide, and DMSO. Chemical imidization with acetic anhydride affords triimide **4**, R = $(CH_2)_6NHAc$, which is highly soluble to organic solvents; however, we have (not surprisingly) been unable to remove the acetyl groups without hydrolyzing the imide group. Inasmuch as the polymerization reaction cannot be conducted in water, a suitably protected, organic soluble derivative of the



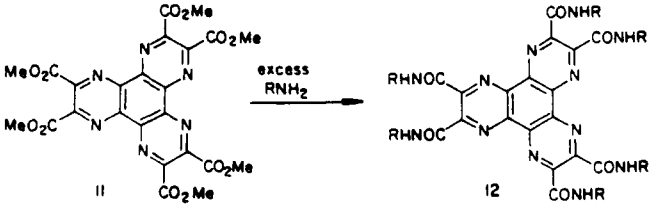


triamic acids was sought. We found that conversion of triester triacid **2** to the corresponding triacid chloride **5** could be accomplished using standard conditions. While the acid chloride was not characterized, conversion to the trimethyl triethyl ester **6** by treatment with ethanol provided both a structure proof for **5** and additional evidence that compound **2** is, in fact, a single isomer.

Reaction of acid chloride **5** with excess dimethylamine provides triester triamide **7** with no apparent further reaction to higher amide derivatives. Compound **7** is a very useful protected version of triester **2**, and therefore of trianhydride **1**. The nmr spectra of **7** are complex, we feel owing to the various conformational isomers that the functional groups of **7** can adopt (*e.g.*, the amide and ester groups can be "above" or "below" the heterocycle plane, *etc.*). Indeed, heating a solution of **7** in DMSO-d_6 results in a coalescence of the amide methyl peaks from a multiplet at 2.95-3.25 ppm (30°) to two broad singlets at 3.07 and 3.18 ppm (130°). Compound **7** affords mixed hexaamides in the reaction with primary diamines; for example, treatment of **7** with 1,6-hexanediamine affords hexaamide **8**, which is soluble in both water and polar organic solvents like acetonitrile and chloroform. We have observed on a small scale that reaction of hexaamide **8** with trifluoroacetic anhydride and heat provides the *N*-trifluoroacetylated triimide as product. Interestingly, **7** is quite unreactive towards substitution by a secondary amine; attempted reaction of **7** with excess dimethylamine returns starting material as the only product. Additionally, reaction of **7** with 1-hexylamine under the same conditions gives only starting material back. Intermediate **7** may also be obtained *via* the *N,N*-dimethylamic acid **9**. Conversion to the *N,N*-dimethylamic acid chloride **10** with thionyl chloride and methanolysis gave triester triamide **7** that was identical to that prepared using the other route. In practice, we find that the sequence **2** → **5** → **7** is the simplest to perform, and is therefore preferable.

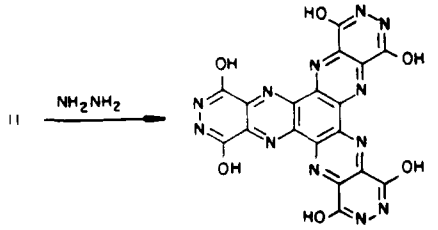


As reported previously, the hexamethyl ester of HAT **11** may be prepared straightforwardly from the hexaacid [3]. Predictably, these ester groups are highly reactive towards acyl substitution reactions. Reaction of **11** with either



a, $R=(CH_2)_5\,CH_3$

b, $R=(CH_2)_9\,CH_3$



1-hexyl- or 1-decylamine provides the corresponding hexaamides **12a** and **12b**. Both compounds are highly insoluble in neutral media (*e.g.*, chloroform, DMF, DMSO), perhaps because of the very favorable amide-amide hydrogen-bonding interaction made possible in a stacked HAT assembly; this hypothesis is being checked by X-ray crystallography.

Finally, reaction of hexaester **11** with hydrazine hydrate affords the corresponding trisphthalhydrazide **13** as a black solid. This compound is soluble in basic aqueous solution, and its ^{13}C nmr spectrum reveals the simple three-line pattern expected for the symmetrical product. Conversion to the trisodium salt with sodium hydroxide again afforded a black solid, which gave appropriate microanalytical data.

EXPERIMENTAL

Mass spectra were obtained by use of a Kratos-30 mass spectrometer. The Ft-nmr spectra at 11.75 tesla (500 MHz) or 7.0 tesla (300 MHz) were obtained using equipment funded in part by NIH Grant #1 S10 RR01458-01A1. We thank Mr. Richard Weisenberger and Mr. Carl Engelman for their assistance in obtaining mass and high-field ^1H nmr spectra, respectively. Melting points were taken on an Electrothermal melting point apparatus and are uncorrected. Microanalyses were carried out at Canadian Microanalytical Service, New Westminster, B. C. Many of the compounds in this series are hygroscopic; satisfactory microanalyses were calculated based on hydrated samples. Perhaps for the same reason, the melting points of some compounds in this series were found to be variable.

2,6,10-Tricarbomethoxy-1,4,5,8,9,12-hexaazatriphenylene-3,7,11-tricarboxylic Acid (**2**).

A mixture of hexaazatriphenylenehexacarboxylic acid [3] (1.5 g, 3 mmoles) in acetic anhydride (40 ml) was heated to 115° briefly to obtain a homogeneous solution. After cooling and evaporation, trianhydride **1** [3] was obtained as an oil that was used without purification. Anhydrous methanol (25 ml) was added, then the solution was concentrated and poured into ice water (25 ml). The solid was filtered, washed with water, and dried *in vacuo* to give triester triacid **2** as a light yellow solid (1.49 g, 92%), mp 205-207° dec; uv (DMSO): 276, 314 nm; ^1H nmr (DMSO-d_6): 4.1 (s, 3H, OCH_3) ppm; ^{13}C nmr (DMSO-d_6): 53.6 (CH_3), 141.9 and 142.3 (internal aromatic carbons), 145.6 and 146.4 (peripheral aromatic carbons), 164.7 and 165.4 (ester and acid carbonyl carbons) ppm; Fab ms: m/e 542 ($M^+ + 2$), 541 ($M^+ + 1$).

Anal. Calcd. for $C_{21}H_{12}N_6O_{12}\cdot 1.5H_2O$: C, 44.55; H, 2.66; N, 14.81. Found: C, 44.27; H, 2.87; N, 14.52.

Tri(*N*-(*n*-hexyl))-1,4,5,8,9,12-hexaazatriphenylene-2,3,6,7,10,11-hexacarboxylic Acid Trisimide (**4a**).

Trianhydride **1**, prepared as described above from the hexaacid (996 mg, 2 mmoles), was dissolved in dry acetonitrile (50 ml) and *n*-hexylamine (2.1 g, 20 mmoles) was added. The yellow precipitate that formed was filtered and washed with acetonitrile. The solid was suspended in water (400 ml), acidified with concentrated hydrochloric acid (10 ml), stirred vigorously for one hour, filtered, washed with water, and dried *in vacuo* to afford triamic acid **3a** (1.4 g, 88%), which decomposes above 180°. The crude amic acid (1.11 g, 1.5 mmoles) was mixed with acetic anhydride (50 ml) and trifluoroacetic acid (0.5 ml), refluxed for 2 hours, and the resulting clear solution was evaporated to dryness. The residue was dissolved in hot toluene, treated with charcoal, filtered, and recrystallized with addition of hexane to give trisimide **4a** (884 mg, 85%), mp 246-248°; uv (DMSO): 288, 338 nm; ^1H nmr (deuteriochloroform): 0.9 (t, 3H, CH_3), 1.35 (m, 6H, 3 x CH_2), 1.85 (quintet, 2H, CH_2), 4.0 (t, 2H, NCH_2) ppm; ^{13}C nmr (deuteriochloroform): 14.0, 22.5, 26.6, 28.4, 31.3, 39.8 (*aliphatic carbons*), 144.6 (*internal aromatic carbons*), 148.8 (peripheral aromatic carbons), 162.0 (carbonyl carbons) ppm; Fab ms: m/e 696 ($M^+ + 3$).

Anal. Calcd for $C_{36}H_{39}N_9O_6$: C, 62.33; H, 5.67; N, 18.17. Found: C, 62.05; H, 5.62; N, 18.14.

Tri(*N*-pentafluorophenyl)-1,4,5,8,9,12-hexaazatriphenylene-2,3,6,7,10,11-hexacarboxylic Acid Trisimide (**4b**).

Trianhydride **1**, prepared as described above from the hexaacid (350 mg, 0.79 mmole) was dissolved in dry dimethylacetamide (15 ml) and treated with pentafluoroaniline (1.43 g, 7.5 mmoles). The mixture was heated on a steam bath for 15 minutes, cooled, poured onto ice (35 g), and acidified with concentrated hydrochloric acid (15 ml). The resulting solid was filtered, washed with water, and dried *in vacuo* at room temperature. The crude triamic acid was mixed with trifluoroacetic anhydride (5 ml) and trifluoroacetic acid (0.3 ml) and heated in a sealed tube on a steam bath for 48 hours. The reaction was evaporated to dryness and the residue was recrystallized/precipitated from ethyl acetate/toluene to afford trisimide **4b** (485 mg, 65%), mp >360°; uv (DMSO): 292, 328 nm; ^{13}C nmr (DMSO-d_6): 135.9, 139.9, 141.1, 145.0 (phenyl carbons; all signals are broad "singlets" or multiplets due to C-F coupling), 144.5 (internal aromatic carbons), 148.6 (peripheral aromatic carbons), 160.6 (carbonyl carbons) ppm; Fab ms: m/e 942 ($M^+ + 3$).

Anal. Calcd. for $C_{36}F_{15}N_9O_6$: C, 46.03; F, 30.34; N, 13.42. Found: C, 46.00; F, 30.22; N, 13.04.

Tri(*N*-*t*-butyl)-1,4,5,8,9,12-hexaazatriphenylene-2,3,6,7,10,11-hexacarboxylic Acid Trisimide (**4c**).

The trianhydride (320 mg, 0.72 mmole), prepared as described above, was treated with a solution of *t*-butylamine (5 ml) in dry acetonitrile (20 ml). After stirring for 1 hour, the reaction was evaporated to dryness. The residue was suspended in acetonitrile, filtered, and washed with acetonitrile to give trisamic acid **3c** (500 mg) as a colorless solid. The crude product was dissolved in thionyl chloride (10 ml) and heated on a steam bath for 30 minutes. Excess thionyl chloride was removed by evaporation, then the residue was dissolved in chloroform and precipitated by addition of hexane. The resulting solid was filtered, washed with hexane and water, then recrystallized from chloroform/hexane with the use of decolorizing carbon to give the trisimide **4c** as a light yellow solid (350 mg, 76%), mp >320°; uv (DMSO): 284, 338; ^1H nmr (deuteriochloroform): 1.85 (s, CH_3); ^{13}C nmr (deuteriochloroform/DMSO-d_6): 28.6 (CH_3), 59.0 (N-*C*(CH_3)$_3$), 144.4 (internal aromatic carbons), 147.8 (peripheral aromatic carbons), 164.8 (carbonyl carbons); Fab ms: m/e 612 ($M^+ + 3$).

Anal. Calcd. for $C_{30}H_{27}N_9O_6\cdot 1.5H_2O$: C, 56.60; H, 4.75; N, 19.80. Found: C, 56.39; H, 4.78; N, 19.48.

2,6,10-Tri(carbethoxy)-3,7,11-tri(carbomethoxy)-1,4,5,8,9,12-hexaazatriphenylene (**6**).

Triester triacid **2** (540 mg, 1 mmoles) in a solution of thionyl chloride (10 ml) and dry benzene (20 ml) was heated on a steam bath for 4 hours and the reaction was evaporated to dryness. The crude triester/triacid chloride **5** was mixed with 15 ml of dry ethanol, upon which a yellow solid immediately separated. The excess alcohol was removed *in vacuo* and the residue was recrystallized from chloroform/hexane to provide hexaester **6** (500 mg, 80%), mp 217-218°; uv (DMSO): 274, 312; ^1H nmr (perdeuterioacetonitrile): 1.46 (t, 3H, CH_2CH_3), 4.11 (s, 3H, OCH_3), 4.57 (q, 2H, CH_2CH_3) ppm; ^{13}C nmr (perdeuterioacetonitrile): 14.4 (C-CH_3), 54.6 (OCH_3), 64.4 (CH_2CH_3), 143.1, 143.2 (internal aromatic carbons), 147.15, 147.21, 147.64, 147.72 (peripheral aromatic carbons), 165.0, 165.5 (carbonyl carbons) ppm; Fab ms: m/e 626 ($M^+ + 2$).

Anal. Calcd. for $C_{27}H_{24}N_6O_{12}$: C, 51.93; H, 3.87; N, 13.46. Found: C, 51.45; H, 3.84; N, 13.38.

2,6,10-Tri(carbomethoxy)-3,7,11-tri(*N*,*N*-dimethylcarboxamido)-1,4,5,8,-9,12-hexaazatriphenylene (**7**).

To a solution of triester triacid chloride **5**, prepared from the hexaacid (500 mg, 1 mmoles) as described above, in dry acetonitrile was added a solution dimethylamine (3 ml) in dry acetonitrile. The resulting solution was stirred for 15 minutes and evaporated to dryness. The crude product was dissolved in acetonitrile, a *little decolorizing carbon* was added and the mixture was passed through a short column of silica gel, eluting with acetonitrile. Evaporation of the eluant gave a light yellow solid (410 mg, 66%), mp 211-212°; uv (DMSO): 286, 322; ^{1}H nmr (deuteriochloroform): 2.99, 3.02, 3.05, 3.10 (rotameric and conformational isomers of one of the amide methyl groups, coalesce on heating to 130°), 3.21, 3.22 (rotameric and conformational isomers of the other amide methyl group; also coalesce at 130°), 4.06, 4.08 (conformational isomers of the ester methyl group) ppm; ^{13}C nmr (deuteriochloroform): 34.99, 35.05 (one of the amide methyl carbons), 38.18, 38.26, 38.32, 38.42 (the other amide methyl carbon), 53.7 (s, ester methyl), 140-167 (complex multiplet for the aromatic and carbonyl carbons) ppm; Fab ms: m/e 623 ($M^+ + 2$).

Anal. Calcd. for $C_{27}H_{27}N_9O_9 \cdot 0.5H_2O$: C, 51.43; H, 4.47; N, 19.99. Found: C, 51.26; H, 4.36; N, 19.71.

Compound **7** could also be made from the anhydride as follows. Trianhydride **1** (444 mg, 1 mmole) was dissolved in freshly distilled dry acetonitrile (100 ml) and dry dimethylamine gas was carefully bubbled into the solution. A yellow solid quickly started separating and addition of the dimethylamine gas was discontinued immediately before the solid started to dissolve. The solid was filtered, washed with acetonitrile, and dried to afford triamic acid **9** that was directly mixed with thionyl chloride (10 ml) and heated on a steam bath for 30 minutes. Excess thionyl chloride was removed *in vacuo* and anhydrous methanol (20 ml) was added. *After 15 minutes methanol was removed in vacuo. Contaminating* dimethylammonium chloride was removed by passage of the reaction mixture through a short column of silica gel using chloroform as eluent to give, after evaporation, triester-triamide **7** with spectral properties identical to those obtained by using the other method.

3,7,11-Tri[*N*-(6-amino)hexyl]carboxamido-2,6,10-tris(*N'*,*N'*-dimethyl)-carboxamido-1,4,5,8,9,12-hexaazatriphenylene (**8**).

To a solution of 1,6-hexanediamine (2.48 g, 21 mmoles) in dry *acetonitrile (100 ml) was added dropwise a solution of triester/triamide* **9** (207 mg, 0.33 mmole) in dry acetonitrile (25 ml). The resulting mixture was heated for 10 minutes over a steam bath then the solvent was removed *in vacuo*, the residue was dissolved in chloroform, and the product was precipitated by adding hexane. This process was repeated several times to remove excess hexanediamine, then the solid was triturated with hexane, filtered, and dried to afford hexaamide **8** (174 mg, 60%), mp >320°, darkens above 290°; uv (DMSO): 286, 326; ^{1}H nmr (deuteriochloroform): 1.3-3.7 (m) ppm; ^{13}C nmr (deuteriochloroform): complicated multiplets in aliphatic and aromatic regions; Fab ms: m/e 875 ($M^+ + 2$).

Anal. Calcd. for $C_{42}H_{53}N_{15}O_6 \cdot 3H_2O$: C, 54.35; H, 7.49; N, 22.63. Found: C, 54.64; H, 7.07; N, 22.40.

2,3,6,7,10,11-Hexa(*N*-(*n*-hexyl))carboxamido-1,4,5,8,9,12-hexaazatriphenylene (**12a**).

To a solution of ester **11** [3] (582 mg, 1 mmole) in 2:1 chloroform/THF (150 ml; solubilized with warming) was added *n*-hexylamine (1.55 g, 15 mmoles) and the mixture was refluxed for 24 hours. The colorless solid that precipitated was filtered, washed with chloroform, and recrystallized from trifluoroacetic acid/water to afford hexaamide **12a** (851 mg, 86%), mp >350°; uv (DMSO): 282, 324 nm; ^{1}H nmr (deuteriochloroform): 0.95 (t, 3H, CH_3), 1.5 (m, 6H, 3 x CH_2), 1.8 (quintet, 2H, CH_2), 3.7 (q, 2H, N-CH_2), 9.2 (br s, NH) ppm; ^{13}C nmr (deuteriochloroform/trifluoroacetic acid): 13.8, 22.4, 26.5, 28.4, 31.3, 42.0 (all single lines, hexyl carbons), 141.6 (s, internal aromatic carbons), 145.4 (s, peripheral aromatic carbons), 164.7 (s, carbonyl carbons) ppm. No identifiable signals were seen by Fab mass spectrometry.

Anal. Calcd. for $C_{54}H_{78}N_{12}O_6 \cdot 0.5H_2O$: C, 64.84; H, 7.96; N, 16.80. Found: C, 64.81; H, 8.33; N, 16.89.

2,3,6,7,10,11-Hexa(*N*-(*n*-decyl))carboxamido-1,4,5,8,9,12-hexaazatriphenylene (**12b**).

To a solution of ester **11** [3] (500 mg, 0.86 mmole) in 1:1 chloroform/dry THF (300 ml) was added *n*-decylamine (3.0 g, 19 mmoles) and the solution was refluxed for 20 hours. The solid that precipitated was filtered, washed with acetonitrile, and dried to afford hexaamide **12b** (*600 mg, 56%*). *Recrystallization from acetonitrile/trifluoroacetic* acid/water and again from trifluoroacetic acid/acetic acid gave the hexaamide as a light brown solid, mp 331-332°; ^{1}H nmr (deuteriochloroform/trifluoroacetic acid): 0.9 (t, 3H, CH_3), 1.2-1.6 (m, 14H, 7 x CH_2), 1.9 (quintet, 2H, CH_2), 3.7 (q, 2H, CH_2), 9.6 (t, 1H, amide NH) ppm.

Anal. Calcd. for $C_{54}H_{78}N_{12}O_6 \cdot 0.5H_2O$: C, 64.84; H, 7.96; N, 16.80. Found: C, 64.81; H, 8.33; N, 16.89.

Hexaazatriphenylene trisphthalhydrazide (**13**).

To a solution of hexaester **11** (582 mg, 1 mmole) in 1:1 chloroform/methanol (100 ml) was added hydrazine hydrate (3 ml), and a black solid quickly formed. The suspension was refluxed for 3 hours, filtered, washed with methanol and chloroform, and dried to afford the trisphthalhydrazide (428 mg, 88%) as a black solid, mp >350°; ^{13}C nmr (triethylamine/deuterium oxide): 160.6 (oxygen bearing *carbon*), 146.4 ("peripheral" HAT carbons), 142.7 (internal aromatic carbons) ppm.

A sample for microanalysis was prepared by dissolving **11** in triethylamine/water and adding an excess of aqueous sodium hydroxide. The precipitate was filtered, washed with methanol, aqueous ethanol, and a small amount of distilled water. The resulting black solid was dried at 110°/1 torr; uv (sodium salt/water): 282, 334, 430 (br) nm.

Anal. Calcd. for the trisodium salt ($C_{18}H_3N_{12}Na_3O_6 \cdot 6H_2O$): C, 32.74; H, 2.29; N, 25.45; Na, 10.44. Found: C, 32.91; H, 2.08; N, 25.22; Na, 10.6.

Acknowledgment.

We thank Ms. Bonnie Grotjohn for technical assistance in obtaining spectral data on some of these compounds. Mass spectra were obtained by use of a Kratos-30 mass spectrometer. The ft-nmr spectra at 11.75 tesla (500 MHz) or 7.0 tesla (300 MHz) were obtained using equipment funded in part by NIH Grand #1 S10 RR01458-01A1. We thank Mr. Richard Weisenberger and Dr. C. E. Cottrell for their assistance in obtaining mass and high-field ^{1}H nmr spectra, respectively, at The Ohio State University Chemical Instrumentation Center and Mr. Carl Engelman for other nmr assistance. Funding from the Army Research Office is acknowledged with gratitude.

REFERENCES AND NOTES

[1] K. Kanakarajan and A. W. Czarnik, "Materials Derived from the Hydrogen-Free Heterocycle Hexaazatriphenylene Hexacarbonitrile. Syntheses and High Temperature Properties of Polyimides", in *Society of Advanced of Materials and Process Engineering Series* **33**, 956 (1988).

[2] For some recent reviews, see: [a] P. E. Cassity, "Thermally Stable Polymers", Marcel Dekker, Inc., New York, NY, 1980, Chapter 5; [b] J. P. Critchley, G. J. Knight, and W. W. Wright, "Heat-Resistant Polymers", Plenum Press, New York, NY, 1983, pp 186-258.

[3] K. Kanakarajan and A. W. Czarnik, *J. Org. Chem.*, **51**, 5241 (1986).

[4] Using the same procedure for the preparation of **4b**, we also *prepared triphenyl trisimide using aniline. The product afforded* ^{13}C *nmr* and mass spectra supportive of the structure assignment; however, because a microanalysis agreeing to within 0.4% on all elements could not be obtained, we are unable to report this compound.

REPRINT

Journal of Synthetic Organic Chemistry

1988
No. 1
January

With Compliments of the Author.

GEORG THIEME VERLAG · STUTTGART · NEW YORK

dehydrogenated with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ). We have shown recently that products **4**, in general, are unstable and cannot be isolated.[3] They hydrolyze to 5,6-dihydropyrimidin-4(3*H*)-ones and polymerize easily. However, this difficulty is avoided if the mixture is quenched at 0 °C with only one equivalent of water and then treated with DDQ at 0 °C. This route gives excellent yields of pyrimidines **5**, including compounds that cannot be obtained in Method A.

The examples cited in Table 1 are representative of the many successful aromatizations of unstable 5,6-dihydropyrimidines conducted at low temperatures by the DDQ method. Recently, we have also reported a similar facile dehydrogenation of 1,6-dihydropyrimidines.[2]

For both Methods A and B it is essential that ethyl ether is used as the medium for the addition reaction. Tetrahydrofuran promotes bromine-lithium exchange and lithiation reactions that result in much lower yields of **5**. Hydrocarbon solvents cannot be used, because of the low solubility of **1** and **2** in these solvents.

Hydrolysis of **5** to uracils **6** is best conducted using 6 normal hydrochloric acid. The conditions employed permit isolation of thienyluracils **6e** and **6f** in good yields. The methoxy group in **6d** is also stable to hydrolysis under these conditions. In agreement with the given, general structures for products **5** and **6**, pyrimidines **5a** and **5c** are hydrolyzed to known 6-methyluracil[4] (**6a**) and 6-phenyluracil[5] (**6c**), respectively. Properties of new pyrimidines **5** and uracils **6** are given in Table 2.

Table 1. Syntheses of Compounds **5c–g** from Pyrimidine **1** (Method A) and Compounds **5a–g** from Pyrimidine **2** (Method B), and Hydrolysis of **5a–g** to Uracils **6a–g**

Reaction of Pyrimidines **1**, **2** with R-Li				Hydrolysis of **5**	
Method	Conditions Temp. Time	Product	Yield (%)	Product	Yield (%)
B	[illegible]	**5a**	85	**6a**	73
B	[illegible]	**5b**	77	**6b**	76
A	[illegible]	**5c**	82	**6c**	79
B	[illegible]	**5c**	83		
A	[illegible]	**5d**	3	**6d**	60
B	[illegible]	**5d**	70		
A	[illegible]	**5e**	40	**6e**	66
B	[illegible]	**5e**	76		
A	[illegible]	**5f**	33	**6f**	75
B	[illegible]	**5f**	76		
A	[illegible]	**5g**	77	**6g**	55
B	[illegible]	**5g**	82		

n-Butyllithium (2.6 M in hexanes), methyllithium (1.4 M in ether), and phenyllithium (1.8 M in cyclohexane/ether) were obtained from Aldrich. 5-Bromo-2,4-bis(methylthio)pyrimidine[6] and 2,4-bis(methylthio)pyrimidine[7] were prepared, and 2-thienyllithium and 2-thiazolyllithium[8] in ether were generated as described. Solutions of 2-methoxyphenyllithium and 3-thienyllithium in ether were generated in the reaction of butyllithium with one mole equivalent of 2-bromoanisole and 3-bromothiophene, respectively. The solution of butyllithium was added dropwise to the ether solution of the respective bromo compound at −40 °C, and the mixture was stirred at −40 °C for 20 min before use. Ether was distilled from sodium benzophenone ketyl immediately before use.

6-Substituted 2,4-Bis(methylthio)pyrimidines 5a–g; General Procedures:

Method A: To a solution of an organolithium reagent R-Li (10 mmol) in ether (50 mL) under nitrogen atmosphere at −40 °C is added

Table 2. Properties[a] of Pyrimidines **5** and Uracils **6**

Compound	mp[b] [°C]	Molecular Formula[c]	^{1}H-NMR[d] δ, J (Hz)	MS[e] m/z (%)
5b	[illegible]	$C_{12}H_{16}N_2S_2$ (228.4)	0.7–2.0 (m, 7H), 2.57 (s + t, 8H); 6.64 (s, 1H, H-5)	228 (16), 199 (11), 186 (100)
5c	74.5–76	$C_{13}H_{14}N_2S_2$ (248.4)	2.59 (s, 3H), 2.62 (s, 3H), 7.19 (s, 1H, H-5), 7.43 (m, 3H), 8.0 (m, 2H, H-2′, H-6′)	248 (100), 233 (27), 215 (44), 202 (24), 187 (21), 128 (44), 77 (34)
5d	74–75	$C_{13}H_{16}N_2OS_2$ (278.4)	2.59 (s, 3H), 2.62 (s, 3H), 3.85 (s, 3H), 6.90–7.45 (m, 3H), 7.54 (s, 1H, H-5), 7.95–8.15 (m, 1H, H-6′)	278 (100), 263 (23), 245 (27)
5f	94–95	$C_{11}H_{10}N_2S_3$ (254.4)	2.56 (s, 3H), 2.59 (s, 3H), 7.00 (s, 1H, H-5), 7.30 (2d, 1H, $J_{3',4'}$ = 3.0, $J_{4',5'}$ = 5.1, H-5′), 7.52 (2d, 1H, $J_{3',4'}$ = 1.3, $J_{4',5'}$ = 5.1, H-4′), 8.02 (2d, 1H, $J_{3',4'}$ = 1.3, $J_{3',5'}$ = 3.0, H-2′)	254 (100), 239 (25), 221 (27)
5g	143–144	$C_{12}H_{13}N_3S_2$ (255.4)	2.56 (s, 3H), 2.60 (s, 3H), 7.43 (d, 1H, $J_{4',5'}$ = 3), 7.57 (s, 1H, H-5), 7.88 (d, 1H, $J_{4',5'}$ = 3)	255 (100), 240 (36), 222 (18), 194 (16), 162 (24), 135 (18)
6b	150.5–151	$C_8H_{12}N_2O_2$ (168.2)	0.7–1.9 (m, 7H), 2.30 (t, 2H), 5.30 (s, 1H, H-5), 10.7 (br s, 2H, NH)	168 (16), 126 (100), 83 (52), 68 (16)
6d	239–240.5	$C_{11}H_{10}N_2O_3$ (218.2)	3.80 (s, 3H), 5.49 (s, 1H, H-5), 6.85–7.65 (m, 4H), 10.78 (br s, 1H, NH), 10.95 (br s, 1H, NH)	218 (100), 160 (96), 104 (42)
6e	> 320	$C_8H_6N_2O_2S$ (194.2)	5.75 (s, 1H, H-5), 7.20 (m, 1H, H-4′), 7.88 (m, 2H, H-3′, H-5′), 11.10 (br s, 2H, NH)	194 (100), 151 (32), 110 (85)
6f	291–293	$C_8H_6N_2O_2S$ (194.2)	5.97 (s, 1H, H-5), 7.62 (m, 2H, H-4′, H-5′), 8.32 (m, 1H, H-2′), 11.98 (br s, 2H, NH)	194 (100), 151 (28), 110 (49)
6g	282–285	$C_7H_5N_3O_2S$ (195.2)	6.10 (s, 1H, H-5), 8.04 (s, 2H, H-4′, H-5′), 11.1 (br s, 2H, NH)	195 (100), 124 (37), 111 (19), 85 (19), 68 (27), 58 (27)

[a] Compounds **5a**, **5e**, **6a**, **6c** [mp Lit. mp (°C): 42, 43/43–45,[10] 101–101.5/101–101.5/313–316, >310,[4] 273–275/272–274,[5] respectively] gave virtually identical ^{1}H-NMR spectra with those of the samples obtained from other sources.

[b] Uncorrected.

[c] Satisfactory microanalyses obtained: C ±0.2, H ±0.1, N ±0.2.

[d] Spectra of pyrimidines **5** and uracils **6** were taken in $CDCl_3$ and DMSO-d_6, respectively, with TMS as internal reference. Varian EM-360 (60 MHz) spectrometer.

[e] Varian MAT 112S spectrometer, at 70 eV.

dropwise a solution of 5-bromo-2,4-bis(methylthio)pyrimidine (1; 2.4 g, 9.6 mmol) in ether (5 mL). The mixture is allowed to react under the conditions given in Table 1. The mixture is then quenched with water (3 mL) in THF (7 mL), and stirred at 23 °C for 0.5 h. The ether layer is separated, the aqueous residue is extracted with CH_2Cl_2 (2 × 10 mL), and the organic solutions containing **5** are combined. Products **5c–g** are isolated by flash chromatography[6] on silica gel eluting with CH_2Cl_2/hexanes (1:3), and recrystallized from hexanes.

Method B: 2,4-Bis(methylthio)pyrimidine (**2**; 1.65 g, 9.6 mmol) is reacted with an organolithium reagent R-Li (10 mmol) under the conditions given in Table 1. The mixture is then quenched with water (0.2 mL, 11 mmol) in tetrahydrofuran (5 mL) at 0 °C, stirred at 0 °C for 30 min and treated with a solution of DDQ (2.7 g, 11.9 mmol) in THF (25 mL). After stirring at 0 °C for 2 h and then at 23 °C for 1 h, the mixture is diluted with ether (50 mL) and extracted with 10% NaOH solution (3 × 25 mL). The organic phase is dried (Na_2SO_4) and concentrated. Products **5a–g** are isolated by chromatography as described in Method A, and recrystallized from hexanes (**5a** and **5c–g**) or distilled in a Kugelrohr apparatus (**5b**, 80 °C/5 Torr).

Uracils 6a–g; General Procedure:

A solution of the appropriate bis(methylthio)pyrimidine **5a–g** (3 mmol) in 6 N HCl (15 mL) is heated at 115 °C for 6 h in a pressure vessel. The acid is then evaporated on a rotary evaporator, and the residue is recrystallized from EtOH. Analytical samples are obtained by drying at 140 °C/0.1 Torr. Compounds **5a–g** are also hydrolyzed within 7 h under reflux conditions. This latter procedure requires frequent removal of crystals of compounds **5a–g** from the reflux condenser.

Financial statements are made to the Petroleum Research Fund, administered by the American Chemical Society. Grant 16598-AC, and to the Research Corporation. Grant CH-383, for support of this research.

Received: 29 May 1987

1. Brown, D. J. *The Pyrimidines*, Wiley-Interscience, New York, 1985.
2. Strekowski, L.; Watson, R. *J. Org. Chem.* **1986**, *51*, 3226; and references cited therein.
3. Strekowski, L.; Watson, R.; Faunce, M. *Synthesis* **1987**, 579.
4. Mąkosza, M.; Łuczak, J. *Synthesis* **1974**, 491.
5. Matsukawa, T.; Ohta, B. J. *J. Pharm. Soc. Jap.* **1950**, *70*, 134.
6. Strekowski, L. *Rocz. Chem.* **1975**, *49*, 1693.
7. Stanovnik, B.; Tišler, M.; Hribar, A.; Barlin, G. B.; Brown, D. J. *Aust. J. Chem.* **1981**, *34*, 1729.
8. Brown, D. J.; Cowden, W. B.; Strekowski, L. *Aust. J. Chem.* **1982**, *35*, 2209.
9. Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
10. Koppel, H. C.; Springer, R. H.; Robins, R. K.; Cheng, C. C. *J. Org. Chem.* **1960**, *26*, 792.

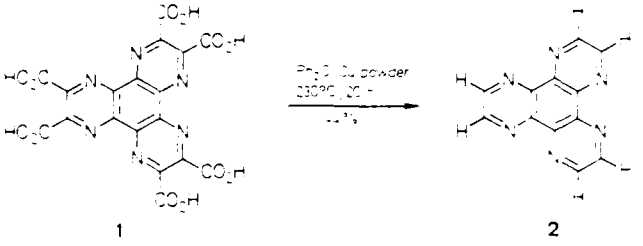
Hexadecarboxylative Synthesis of Hexaazatriphenylene

Mary P. Sarna, Antoni W. Czarnik*

Department of Chemistry, The Ohio State University, Columbus, OH 43210, USA

Thermal decarboxylation of hexaazatriphenylene hexacarboxylic acid (**1**) in diphenyl ether (230 °C, 20 h) with added copper powder affords the parent heterocycle, hexaazatriphenylene, in 44% yield after filtration through an alumina plug.

Hexaazatriphenylene (**2**; abbreviated HAT) is a highly symmetrical heterocycle first synthesized by Nasielski-Hinkens *et al.* that has been used to prepare polynuclear chromium carbonyl complexes.[1] This ligand, while of potential utility in the synthesis of other polynuclear complexes, has not until recently become readily accessible. The original synthesis[1] is on the order of ten steps long. A shorter route was conceived by Kohne and Praefcke as proceeding from a triple condensation of glyoxal with the known hexaaminobenzene (HAB), but this reaction lead to HAT in only very low yield (related hexaalkyl derivatives could be obtained in good to excellent yield however).[2] Most recently, Rogers has reported that this reaction can be accomplished in good yield by using a modification of this procedure.[3] This most recent paper prompts us to describe our own method for the synthesis of HAT at this time. While the method described using HAB as starting material is a valuable one, it does suffer from the disadvantage that the immediate precursor to HAB, namely 1,3,5-triamino-2,4,6-trinitrobenzene, is a military explosive and potentially subject to detonation. Under some circumstances, this may be an unacceptable drawback.



1 2

We now report that HAT may be prepared *via* the hexadecarboxylation of HAT(COOH)$_6$ (**1**), a compound whose synthesis we have reported *via* a three-step sequence.[4] Thermal decarboxylations of heterocyclic α-carboxylic acids have long been reported as preparatively useful in, for example, the pyrazine series: the mono-, di-, tri-, and tetracarboxylic acid derivatives of 1,4-pyrazine all afford pyrazine itself under appropriate conditions.[5] While a variety of conditions have been employed for this general reaction (e.g., heating in dibutyl phthalate, glacial acetic acid, or other solvents) and examined by us, the decarboxylation of hexaacid **1** occurs best in diphenyl ether with added copper powder. Heating under these conditions at 230 °C for 20 h in an inert atmosphere affords HAT in 44% yield after filtration through an alumina plug. The resulting solid sample is identical to HAT prepared as previously described in every respect, and is of analytical purity.

This route, which is four steps from commercially available precursors, does not involve the intermediacy of potentially explosive precursors and may be preferable to that reported recently[3] in some situations.

1,4,5,8,9,12-Hexaazatriphenylene (2):

A mixture of hexaazatriphenylene hexacarboxylic acid[4] (**1**; 1.0 g, 4.2 mmol), copper powder (0.2 g), and freshly distilled diphenyl ether (25 mL) is stirred at 230 °C for 20 h under a dry nitrogen atmosphere. The reaction is then cooled and filtered, and the solid is washed with hexane (3 × 50 mL) to remove adsorbed diphenyl ether. The crude solid sample is added to the top of a short column of neutral alumina and eluted with $CHCl_3$. The single band is collected and the solvent evaporated to afford **2** as a light yellow solid; yield: 210 mg (44%); mp > 360 °C (Lit.[1] mp > 350 °C).

The product is identical to an authentic sample[3] in all respects.

$C_{12}H_6N_6$	calc.	C 61.53	H 2.58	N 35.88
(234.2)	found	61.20	2.68	35.77

Funding for this work was a grant from the Army Research Office is acknowledged with gratitude.

Received: 15 April 1987, revised: 13 July 1987

(1) Nasielski-Hinkens, R., Benedek-Vamos, M., Maetens, D., Nasielski, J. *J. Organometal. Chem.* **1981**, *217*, 179.
(2) Kohne, B., Praefcke, K. *Liebigs Ann. Chem.* **1985**, 522.
(3) Rogers, D. *Z. J. Org. Chem.* **1986**, *51*, 3904.
(4) Kanakaraian, K., Czarnik, A. W. *J. Org. Chem.* **1986**, *51*, 5241.
(5) Barlin, G. B. *The Pyrazines*, John Wiley & Sons 1982, pp 253–258 [volume 41 in the series, *The Chemistry of Heterocyclic Compounds*, Weissberger, A., Taylor, E. C. (eds.)].

A Facile and Versatile Synthesis of 2-Substituted Tryptophans as N^{α}-*tert*-Butyloxycarbonyl Derivatives

J. P. Li, Kenneth A. Newlander,* Tobias O. Yellin

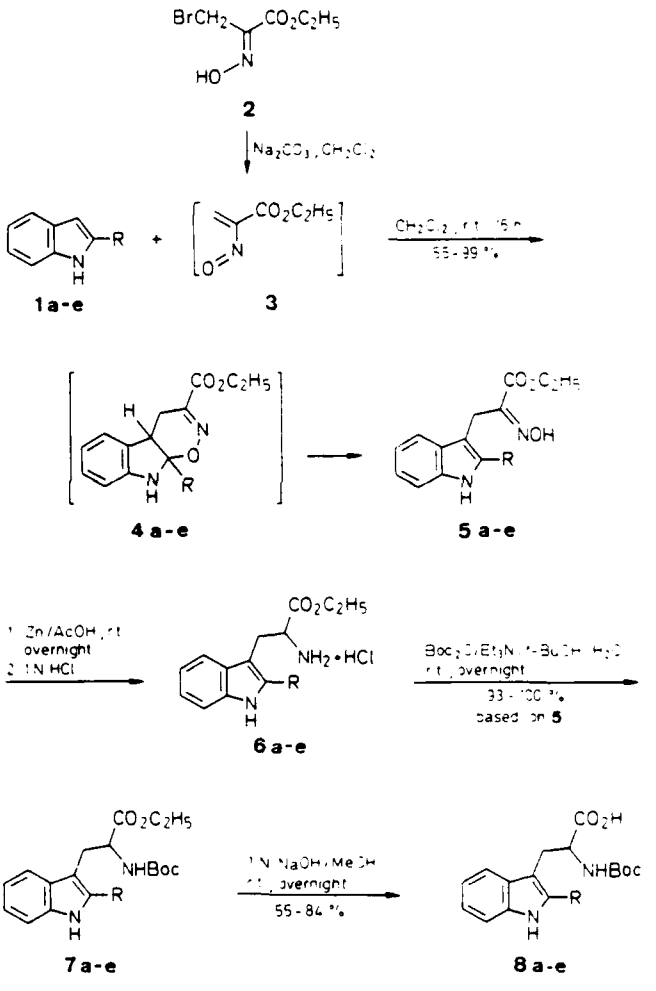
Smith Kline Beckman Corporation, Department of Peptide Chemistry, 2050 Page Mill Road, Palo Alto, CA 94304, USA

Diels-Alder type cycloaddition between 2-substituted indoles and ethyl α-nitrosoacrylate followed by reduction affords 2-substituted tryptophan esters. N-Protection followed by saponification furnishes the corresponding N^{α}-protected 2-substituted tryptophans suitable for peptide synthesis. The preparation of a number of 2-substituted indoles by modified Madelung synthesis is also described.

Only a small number of 2-substituted tryptophans or their derivatives have been reported in the literature. Interestingly, this handful of compounds represents a considerable variety of substituents: alkyl (methyl,[3,4] *tert*-butyl[5]), aryl (phenyl[6]), carboxyl,[7–9] hydroxyl,[9–14] thiol,[11] thioether,[15,16] and halogen.[17] We were interested in using a bulky substituent (alkyl or aryl) in the 2-position of the indole nucleus to restrict the conformation of the side chain of tryptophan in peptides. Among the 2-substituted tryptophans of interest to us, the 2-*tert*-butyl and 2-phenyl analogs are known compounds.

N^{α}-benzyloxycarbonyl-2-*tert*-butyltryptophan benzyl ester was obtained in 2–3% yields among other butylated products by direct alkylation of the N-protected tryptophan ester.[5] The synthesis of racemic 2-phenyltryptophan was achieved by Kissman and Witkop[6] by four variations of the "gramine" synthesis. In our hands, however, none of the above approaches gave satisfactory results as a practical preparative procedure. We wish to report in this paper a general and facile method for the preparation of 2-substituted tryptophans as their N^{α}-protected derivatives, suitable for peptide synthesis.

We have adopted the elegant cycloaddition reaction of Gilchrist et al.[18,19] to construct the skeletons of the desired 2-alkyl- or 2-aryl-tryptophans.[20] Thus, Diels-Alder type cycloaddition between 2-substituted indole **1** and the transient nitrosoalkene **3**, which was generated *in situ* from ethyl 3-bromo-2-hydroxyiminopropanoate (**2**), afforded the oxime **5** after ring opening and bond rearrangement of the adduct **4**. Since **5** may further react with another molecule of **3** to form a 2:1 adduct,[21] a two- to three-fold excess of indole **1** was usually used to suppress adduct formation. The unreacted indole **1** was easily separated from the oxime **5** and recovered by column chromatography on silica gel. Reduction of **5** with zinc in acetic acid followed by conversion to its hydrochloride salt gave the 2-substituted tryptophan ester hydrochloride **6** in excellent yields. Without further purification, **6** was converted to the N^{α}-protected derivative **7**.[22] Saponification followed by acidification furnished the 2-substituted N^{α}-Boc-tryptophan **8**, which was suitable for peptide synthesis by solid phase or solution methods. Compounds **8b, d, e** were oils. They were converted to the solid dicyclohexylamine salts for characterization.



Boc = *t*-C_4H_9OCO

1, 4–8	R	1, 4–8	R
a	C_6H_5	**d**	*t*-C_4H_9
b	$C_6H_5CH_2$	**e**	2-pyridyl
c	*c*-C_6H_{11}		

Of the starting 2-substituted indoles, **1a** is commercially available, and **1e**[23,24] was prepared by the Fischer indole synthesis according to a reported procedure.[23] In our hands Fischer synthesis of **1d**[25] using zinc chloride or polyphosphoric acid afforded an impure product which was difficult to purity. The method we chose for the preparation of **1d** was a modified

Madelung indole synthesis.[26-28] Pure **1d** was obtained from readily available trimethylacetyl chloride and *o*-toluidine in a short time in practically quantitative yield, as reported.[27,28]

Compounds **1b**[29,30] and **1c**[31,32] has been synthesized by various methods. However, all of these methods were either nonspecific, tedious, or required unusual reaction conditions. Using the modified Madelung synthesis[26-28] as mentioned above, **1c** was obtained in 65% yield and the unreacted *N*-cyclohexylcaronyl-*o*-toluidine could be recovered. Excess *n*-butyllithium or prolonged reaction time did not drive the reaction to completion. In an attempt to prepare **1b** by this modified Madelung method, however, *N*-phenylacetyl-*o*-toluidine remained unchanged under various conditions and was recovered quantitatively. This difficulty was overcome by utilizing the method of Le Corre et al.[33]

Indeed, by adopting Le Corre's method, compounds **1b** and **1c** were successfully prepared.

This synthetic sequence involved the initial formation of the phosphonium chloride **10** from *o*-nitrobenzyl chloride (**9**) and triphenylphosphine. Compound **10** was best reduced with zinc in acetic acid to the aniline hydrochloride **11**. Reduction using stannous chloride hydrochloric acid resulted in laborious work-up and impure product, and reduction with Raney nickel and anhydrous hydrazine in methanol led to *o*-toluidine exclusively. Acylation of **11** with appropriate acyl chlorides in the usual manner afforded the required precursors **12**. Treatment of **12** with potassium *tert*-butoxide led to the 2-substituted indoles **1** in yields of 38% (**1c**) to 65% (**1b**).

In conclusion, the overall processes as described above provide for a facile and versatile procedure for the synthesis of a variety of 2-substituted tryptophan derivatives.

Table. Indoles **5** and 2-Substituted Tryptophans **7** and **8** Prepared

Product	Yield (%)[a]	mp (°C) (solvent)	Molecular Formula[b]	TLC (R_f)[c]	^{1}H-NMR (TMS)[d] δ, *J* (Hz)
5a	73	142–143	$C_{19}H_{14}N_2O_3$ (322.4)	0.50	($CDCl_3$) 1.05 (t, 3H, *J* = 7); 4.04 (q, 2H, *J* = 7); 4.2 (s, 2H); 6.9–7.8 (m, 9H); 8.09 (br s, 1H); 10.0 (s, 1H)
5b	84	166–167	$C_{20}H_{20}N_2O_3$ (336.4)	0.58	($CDCl_3$) 1.22 (t, 3H, *J* = 7), 4.1 (s, 2H); 4.16 (q, 2H, *J* = 7); 4.22 (s, 2H), 6.9–7.9 (m, 5H); 7.21 (s, 5H); 9.67 (s, 1H)
5c	79	89–90	$C_{19}H_{24}N_2O_3$ (328.4)	0.55	($CDCl_3$) 1.25 (t, 3H, *J* = 7); 1.1–2.1 (m, 10H); 2.8–3.4 (m, 1H); 4.05 (s, 2H); 4.17 (q, 2H, *J* = 7); 6.9–7.4 (m, 3H); 7.6–8.1 (m, 2H); 10.4 (s, 1H)
5d	55	(syrup)	$C_{17}H_{22}N_2O_3$ (302.4)	0.70	($CDCl_3$) 1.07 (t, 3H, *J* = 7); 1.5 (s, 9H); 4.05 (q, 2H, *J* = 7, 2H); 4.27 (s, 2H); 6.9–7.7 (m, 4H); 8.0 (br s, 1H); 10.1 (br s, 1H)
5e	60	124 dec ($CHCl_3$)	$C_{18}H_{17}N_3O_3$ (323.4)	0.64	(CMF-*d*$_7$) 0.95 (t, 3H, *J* = 7); 3.98 (q, 2H, *J* = 7); 4.48 (s, 2H); 6.8–8.1 (m, 8H); 8.73 (br d, 1H, *J* = 5); 11.5 (s, 1H)
7a	95	(noncrystal. solid)	$C_{24}H_{28}N_2O_4$ (408.49)	0.79	($CDCl_3$) 1.0 (t, 3H, *J* = 7); 1.3 (s, 9H); 3.4 (d, 2H, *J* = 6); 3.7 (q, 2H, *J* = 7); 4.54 (m, 1H); 4.9 (br d, 1H); 6.9–7.9 (m, 9H); 8.35 (br s, 1H)
7b	100	(noncrystal. solid)	$C_{28}H_{30}N_2O_4$ (422.5)	0.74	($CDCl_3$) 1.08 (t, 3H, *J* = 7); 1.39 (s, 9H); 3.23 (d, 2H, *J* = 5.5, 2H); 4.0 (q, *J* = 7, 2H); 4.0 (s, 2H); 4.67 (m, 1H); 5.12 (br d, 1H); 6.86–7.63 (m, 4H); 7.18 (s, 5H); 8.1 (br s, 1H)
7c	83	(noncrystal. solid)	$C_{24}H_{34}N_2O_4$ (414.5)	0.72	($CDCl_3$) 1.1 (t, 3H, *J* = 7); 1.4 (s, 9H); 1.1–2.1 (m, 10H); 2.5–3.0 (m, 1H); 3.23 (d, 2H, *J* = 5); 4.08 (q, 2H, *J* = 7); 4.4–4.8 (m, 1H); 4.9–5.3 (m, 1H); 6.8–7.7 (m, 4H); 8.62 (br s, 1H)
7d	95	(syrup)	$C_{22}H_{32}N_2O_4$ (388.5)	0.76	($CDCl_3$) 1.0 (t, 3H, *J* = 7); 1.3 (s, 9H); 1.5 (s, 9H); 3.3 (d, 2H, *J* = 7); 4.0 (q, 1H, *J* = 7); 4.58 (m, 1H); 5.13 (br d, 1H); 6.9–7.6 (m, 5H); 8.2 (br s, 1H)
7e	90	196 dec ($CHCl_3$-EtOAc)	$C_{23}H_{27}N_3O_4$ (409.5)	0.75	(DMF-*d*$_7$) 1.05 (t, 3H, *J* = 7); 1.3 (s, 9H); 3.5 (d, 2H); 4.0 (q, 2H, *J* = 7); 4.1–4.55 (m, 1H); 7.0–8.2 (m, 9H); 8.7 (br d, 1H, *J* = 5)
8a	84	197–198 (EtOAc)	$C_{22}H_{24}N_2O_4$ (380.4)	0.36	(DMF-*d*$_7$) 1.3 (s, 9H); 3.4 (d, 2H, *J* = 6); 4.55 (m, 1H); 5.3 (br d, 1H); 6.9–7.9 (m, 10H); 10.5 (s, 1H)
8b[e]	73	186–188 (Et_2O)	$C_{38}H_{49}N_3O_4$ (575.8)	0.49	–
8c	82	212–213 (EtOAc)	$C_{22}H_{30}N_2O_4$ (386.5)	0.55	(DMF-*d*$_7$) 1.35 (s, 9H); 1.2–2.2 (m, 10H); 2.9 (m, 1H); 3.27 (d, 2H); 4.44 (m, 1H); 6.59 (d, 1H, *J* = 8.5); 6.9–7.75 (m, 5H)
8d[e]	60	210–212 (Et_2O)	$C_{32}H_{31}N_3O_4$ (541.8)	0.26	
8e[e]	55	199–200 (Et_2O)	$C_{33}H_{46}N_4O_4$ (562.8)	0.30	

[a] Yields of **7** based on oxime **5**

[b] Satisfactory microanalyses obtained: C ±0.4%, H, N ±0.3%

[c] Analtech Uniplate silica gel GF-250 micro scored plates in $CHCl_3$ MeOH AcOH (95 4 1 by volume). Spots were visualized under UV light (254 nm) and by Erhlich and ninhydrin sprays.

[d] Obtained in a Varian EM 360A spectrometer

[e] Isolated and characterized as dicyclohexylamine salt.

Synthesis - VC 186/11/87/682 Comm., planed for 7/88, 1 2

Nitrosations in Anhydrous Trifluoroacetic Acid Media: A Modification for Insoluble or Deactivated Amine and Amide Precursors

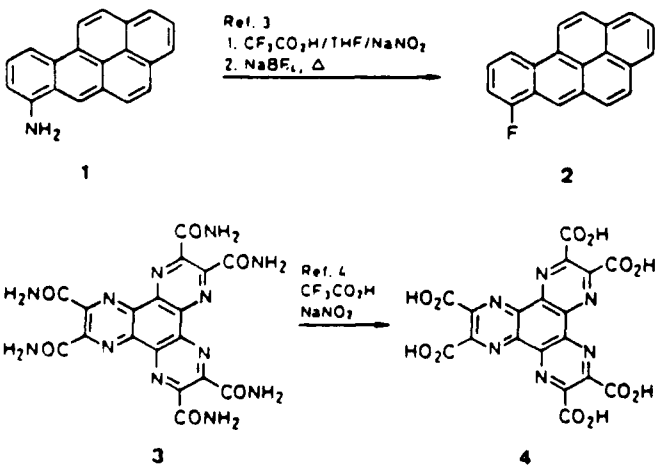
K. Kanakarajan,* Karl Haider, Anthony W. Czarnik

Department of Chemistry, The Ohio State University, Columbus, Ohio 43210, USA

Nitrosation reactions can be accomplished cleanly in anhydrous trifluoroacetic acid as solvent, which permits the use of both deactivated and insoluble amines and amides as starting materials.

The nitrosation of amines with sodium nitrite to afford the corresponding diazonium salts is one of the most versatile reactions in organic chemistry. Over the past several years, we have found that some amines are not amenable to nitrosation using the conditions found most commonly in the literature, e.g., sodium nitrite in aqueous mineral acids. Problems of this type are seen when the starting amine is either deactivated by strongly electron-withdrawing groups at adjacent or conjugated positions, or when the starting amine is extraordinarily insoluble. Especially vigorous nitrosation conditions have been used previously with deactivated amine starting materials; such variations include the use of concentrated sulfuric acid, mixtures of sulfuric and acetic or phosphoric acids, concentrated nitric acid, and the use of organic cosolvents.[1] We now report that nitrosation reactions can be accomplished cleanly in anhydrous trifluoroacetic acid (TFA) solvent, and that this reaction medium allows the use of both deactivated and insoluble amines and amides as starting materials.

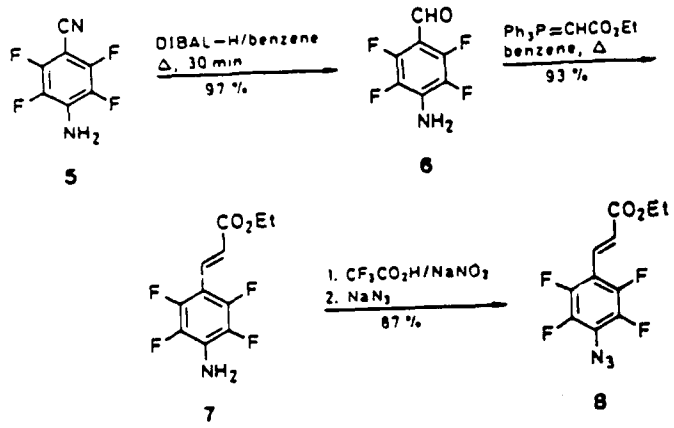
Two examples of difficult nitrosations that have been carried out successfully in TFA have been reported previously by one of us (KK) in the context of other projects. For example, nitrosation of the weakly basic 7-aminobenzo[*a*]pyrene (**1**) in aqueous acid followed by treatment with tetrafluoroboric acid and thermolysis is not successful in the synthesis of 7-fluorobenzo[*a*]pyrene (**2**). An anhydrous modification using dry gaseous nitric oxide was similarly unsuccessful.[2] However, dissolution of amine **1** in anhydrous TFA/tetrahydrofuran occurred readily, and nitrosation proceeded smoothly; subsequent decomposition of the tetrafluoroborate salt afforded the desired fluoride (Scheme A).[3] In addition, we have reported that hydrolysis of hexaamide **3** to the corresponding hexaacid **4** is incomplete under strongly acidic or basic conditions; a classic nitrosation-mediated hydrolysis likewise afforded a mixture of partially hydrolyzed polyacids. Dissolution of hexaamide **3** in TFA is complete, and addition of sodium nitrite followed by water gave the desired hexaacid **4** in excellent yield[4] (Schema A).



1 **2** **3** **4**

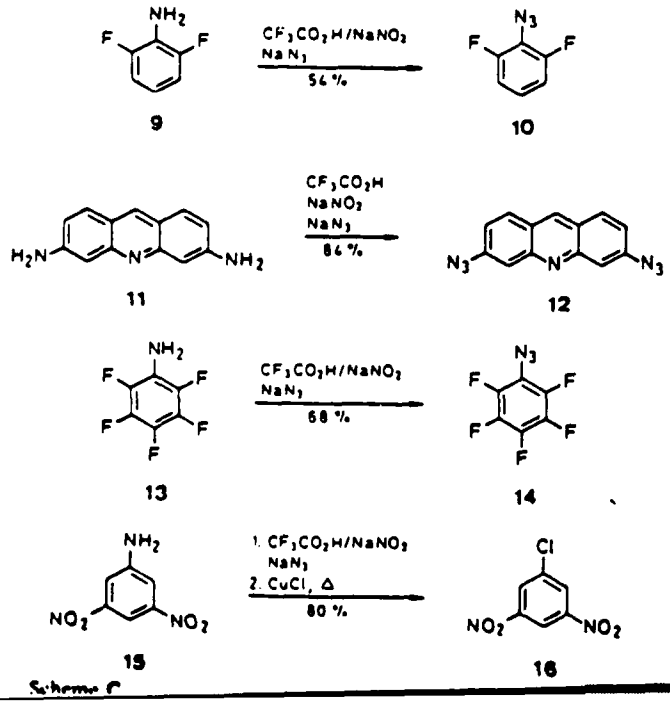
Scheme A

We have carried out several other difficult diazotization reactions in TFA to demonstrate the generality of this modification. Ethyl 4-amino-2,3,5,6-tetrafluorocinnamate (7) is prepared by diisobutylaluminum hydride (DIBAL-H) reduction of 4-amino-2,3,5,6-tetrafluorobenzonitrile (5) to the corresponding aldehyde 6 followed by a Wittig reaction with (elhoxycarbonylmethylene)triphenylphosphorane. Diazotization of ethyl 4-amino-2,3,5,6-tetrafluorocinnamate (7), which is insoluble in aqueous acid, is affected in anhydrous TFA to afford the product azide 8 in 87% yield after treatment with sodium azide (Scheme B). Likewise, 2,6-difluoroaniline[6] (9) is converted to 2,6-difluorophenyl azide (10; 54%) and 3,6-diaminoacridine[5] (11) is converted to 3,6-diazidoacridine (12; 84%) (Scheme C).



Scheme B

For the purposes of comparison, we have carried out the diazotization of pentafluoroaniline (13) under both aqueous and TFA conditions. Attempted diazotization in 5N hydrochloric acid with sodium nitrite, followed by reaction in the cold with sodium azide and extraction with ether afforded only the starting material and several unidentified components that were not the aryl azide 14 as determined by GC comparison with an authentic sample. While the failure of pentafluoroaniline in this reaction has not been explicitly reported previously, the literature route involves conversion of hexafluorobenzene to pentafluorophenylhydrazine followed by conversion to the azide.[8] By comparison, the reaction of pentafluoroaniline with sodium nitrite in TFA, followed by treatment with sodium azide, gave pentafluorophenyl azide (14) directly as a yellow oil in 68% yield, identical with an authentic sample (Scheme C).



Scheme C

The Sandmeyer reaction may likewise be carried out using TFA as solvent. The conversion of 3,5-dinitroaniline (15) to 1-chloro-3,5-dinitrobenzene (16) is accomplished in 80% yield, which is a modest improvement over a previously reported diazotization method using nitrosyl sulfuric acid[7] (Scheme C).

In summary, diazotization of aryl amines in anhydrous TFA offers a useful variation on this well-known reaction for insoluble or deactivated starting materials. While TFA itself is a relatively expensive solvent, its use provides an alternative in cases for which direct reaction of the amine is desirable.

Melting points were taken on an Electrothermal melting point apparatus and are uncorrected. Microanalyses were carried out at Canadian Microanalytical Service, New Westminster, B.C. Mass spectra were obtained by use of a Kratos-30 mass spectrometer. FT-NMR spectra at 11.75 tesla (500 MHz) or 7.0 tesla (300 MHz) were obtained using equipment funded in part by NIH Grant #1 S10 RR01458-01A1. We thank Mr. Richard Weisenberger and Dr. C.E. Cottrell for their assistance in obtained mass and high-field ^{1}H-NMR spectra, respectively, at The Ohio State University Chemical Instrumentation Center, and Mr. Carl Engelman for other NMR assistance. All starting materials were commercial products.

Ethyl (*E*)-4-Amino-2,3,5,6-tetrafluorocinnamate (7):
4-Amino-2,3,5,6-tetrafluorobenzonitrile (5; 3.8 g, 20 mmol) is dissolved in dry benzene (250 mL). To this solution, a 1.5 M toluene solution of DIBAL-H (40 ml, 60 mmol) is added dropwise over 30 min. The resulting mixture is stirred for 10 h, and then decomposed by adding methanol (20 mL). The organic solution is washed with water, dried ($MgSO_4$), and the solvent is removed *in vacuo* to give 6 as a colorless solid; yield: 3.72 g (97%); mp 110–111 °C. [IR (CCl_4): ν = 1720, 3430, 3530 cm^{-1}; MS: *m/z* (%) = 193 (98%, M^+), 192 (100%, $[M-1]^+$].

The crude aldehyde 6, (1.92 g, 10 mmol) and (ethoxycarbonylmethylene)triphenylphosphorane (3.84 g, 11 mmol) are mixed in dry benzene (100 mL) and refluxed for 10 h. The solvent is removed *in vacuo* and the residue is chromatographed using a silica gel column and eluting with CH_2Cl_2. Ethyl (E)-4-amino-2,3,5,6-tetrafluorocinnamate (7) elutes in the first fractions; evaporation gives a colorless solid; yield: 2.25 g (93%); mp 126–127 °C.

$C_{11}HgF_4NO_2$	calc.	C 50.20	H 3.45	N 5.32
(263.2)	found	50.12	3.39	5.46

IR (CCl_4): ν = 1670, 1730, 3440, 3530 cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ = 1.31 (t, 3, CH_3, J = 7.1 Hz); 4.25 (q, 2, CH_2, J = 7.1 Hz); 4.38 (br s, 1.8, NH_2); 6.55 (d, 1, CH, J = 16.4 Hz); 7.69 (d, 1, CH, J = 16.4 Hz).

^{13}C-NMR ($CDCl_3$): δ = 14.2 (s), 60.6 (s), 101.9 (t), 121.8 (t), 128.0 (tt), 129.9 (s), 134.3 (m), 138.1 (m), 143.8 (m), 147.8 (m), 166.9 (s)

^{19}F-NMR ($CDCl_3$): δ = −167.19 (m), −146.962 (m).

MS: *m/z* (%) = 264 (30%, $[M+1]^+$); 263 (65%, M^+).

Ethyl (*E*)-4-Azido-2,3,5,6-tetrafluorocinnamate (8):
Ethyl 4-amino-2,3,5,6-tetrafluorocinnamate (7; 263 mg, 1 mmol) is dissolved in TFA (4 mL). The resulting orange solution is cooled in an ice bath and solid $NaNO_2$ (276 mg, 4 mmol) is added in portions over a period of 5 min with stirring. To the resulting green solution, solid $NaNO_2$ (195 mg, 3 mmol) is added over a 5 min period. The mixture is stirred for 10 min, then poured onto 20 g of ice. The mixture is extracted with CH_2Cl_2 (3 × 30 mL), the organic phase is washed with water (3 × 25 mL) and aq. $NaHCO_3$ solution (20 mL). The organic layer is dried ($MgSO_4$), concentrated under vacuum, and passed through a short column of neutral alumina. Evaporation of the solvent gives 8 as a colorless solid; yield: 251 mg (87%); mp 67–68 °C.

$C_{11}H_7F_4N_3O_2$	calc.	C 45.69	H 2.44	N 14.53
(289.2)	found	45.89	2.42	14.58

IR (KBr): ν = 3000, 2100, 1700 cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ = 1.4 (t, 3, CH_3, J = 7.1 Hz); 4.3 (q, 2, CH_2, J = 7.1 Hz); 6.7 (d, 1, CH, J = 16.4 Hz); 7.6 (d, 1, CH, J = 16.4 Hz).

^{13}C-NMR ($CDCl_3$): δ = 14.1 (s), 61.0 (s), 110.0 (t), 121.0 (t), 125.8 (t), 128.4 (s), 138.6 (m), 142.5 (m), 143.5 (m), 147.4 (m), 166.0 (s).

^{19}F-NMR ($CDCl_3$): δ = −156.55 (m), −144.593 (m).

MS: *m/z* = 289 (M^+)

2,6-Difluorophenyl Azide (10):
2,6-Difluoroaniline (9; 2.0 g, 15 mmol) is dissolved in TFA (20 mL) and cooled in an ice bath. Solid $NaNO_2$ (1.07 g, 15 mmol) is added in portions with stirring over 5 min. NaN_3 (1.01 g, 15 mmol) is added to the diazotized solution and the resulting mixture is stirred for an additional 30 min. Water (15 mL) is added, and the product is extracted into ether (3 × 20 mL), washed with 10% aq. NaOH solution, water, and dried ($MgSO_4$). The solvent is removed under vacuum, the residue is redissolved in hexane and is passed through a short column of neutral alumina using hexane as eluent to afford the azide 10 as pale yellow crystals; yield: 1.3 g (54%); bp 45°C/3 mbar [Lit.[6] bp not reported].

^{1}H-NMR ($CDCl_3$): δ = 6.9–7.1 (m, ArH).

MS: *m/z* = 155 (M^+).

3,6-Diazidoacridine (12).
3,6-Diaminoacridine hydrochloride (11; 500 mg, 2.4 mmol) is dissolved in TFA (15 mL) and stirred at 0–5°C for 10 min. Solid $NaNO_2$ (600 mg, 8.7 mmol) is added in portions over a period of 5 min, then the solution is stirred for additional 5 min and NaN_3 (1.6 g, 25 mmol) is added with efficient stirring to avoid foaming. After 15 min, water (20 mL) is added to precipitate the product, which is filtered, washed with water (3 × 15 mL), and dried *in vacuo* to give of 12 as an orange solid; yield: 530 mg (84%). The product is recrystallized from EtOAc/hexane to give orange crystals, mp 167–168°C (dec) [Lit.[5] 168–169 C (dec)].

^{1}H-NMR (CD_3OD): δ = 7.48 (dd, 2, J = 10, 2 Hz); 7.65 (d, 2, J = 2 Hz); 8.31 (d, 2, J = 10 Hz); 9.45 (s, 1, central ring CH).

MS: *m/z* = 261 (M^+).

Pentafluorophenyl Azide (14):
Pentafluoroaniline (13; 1.4 g, 7.7 mmol) is dissolved in TFA (20 mL) and cooled to −10 C. Solid $NaNO_2$ (1.05 g, 15 mmol) is added in portions over a 20 min period with stirring. NaN_3 (1.05 g, 16 mmol) is added over 5 min and the solution is stirred for 1 h. The mixture is diluted with distilled water (30 mL) and the product is extracted with ether (3 × 20 mL). The combined extract is washed with sat. $NaHCO_3$ solution and dried ($MgSO_4$). Solvent removal under vacuum followed by Kugelrohr distillation (4 mbar, bath temperature of ca. 30°C) affords 14 as a pale yellow oil (1.1 g, 68%). This sample is indistinguishable from an authentic sample of pentafluorophenyl azide[8] as determined by GC comparison and by ^{13}C-NMR spectrometry.

^{13}C-NMR ($CDCl_3$): δ = 136.2, 136.3, 139.2, 140.2, 143.2.

MS: *m/z* = 209 (M^+).

1-Chloro-3,5-dinitrobenzene (16):
3,5-Dinitroaniline (15; 550 mg; 3 mmol) is dissolved in TFA (10 mL) and cooled to 10 C. Solid $NaNO_2$ (414 mg, 6 mmol) is added in portions with stirring. Within a few minutes a clear, light green solution of the diazonium salt is obtained. The diazonium salt solution is added dropwise to an ice-cold solution of CuCl (1.0 g, 11 mmol) in conc. HCl (10 mL) over 10 min with efficient stirring. A yellow precipitate formed redissolved upon the addition of water (200 mL). The clear solution is heated on a steam bath for 15 min, cooled, and extracted with EtOAc (3 × 100 mL). The organic phase is washed with water (3 × 50 mL), dried ($MgSO_4$), and the solvent is removed to give an oil. Chromatography on neutral alumina using $CHCl_3$ as the eluant followed by recrystallization from hexane gives 16 as colorless needles; yield: 485 mg, (80%); mp 54–54.5 C (Lit.[7] mp 54–54.5°C).

^{1}H-NMR ($CDCl_3$): δ = 8.55–8.95 (m, ArH).

^{13}C-NMR ($CDCl_3$): δ = 117.2, 129.2, 137.0, 148.9.

MS: *m/z* (%) = 202 (100, M^+ for ^{35}Cl isotope); 204 (70, M^+ for ^{37}Cl isotope).

Funding from the Army Research Office is acknowledged with gratitude. We also thank Professors Melvin Newman and Matthew Platz for their support during various stages of this work.

Received: 12 November 1987; revised: 11 March 1988

(1) Godovikova, T.I., Rakitin, O.A., Khmel'nitskii, L.I. *Usp. Khim.* **1983**, *52*, 777; *Russ. Chem. Rev.* (Engl. Transl.) **1983**, *52*, 440.
(2) Newman, M.S., Lilje, K.C. *J. Org. Chem.* **1979**, *44*, 1347.
(3) Newman, M.S., Khanna, V.K., Kanakarajan, K. *J. Am. Chem. Soc.* **1979**, *101*, 6788.
(4) Kanakarajan, K., Czarnik, A.W. *J. Org. Chem.* **1986**, *51*, 5241.
(5) Firth, W., Yielding, L.W. *J. Org. Chem.* **1982**, *47*, 3002.
(6) Leyva-Ramos, E. *Ph.D. Thesis*, The Ohio State University, 1986.
(7) Welsh, L.H. *J. Am. Chem. Soc.* **1941**, *63*, 3276.
(8) Birchall, J.M., Hazeldine, R.N., Parkinson, A.R. *J. Chem. Soc.* **1962**, 4966.